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THE MEDICAL CLINICS OF NORTH AMERICA

VOLUME 4 NUMBER 1

CLINIC OF DR. NELLIS B. FOSTER

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NEPHRITIS

DR. FOSTER: You have from time to time asked me rather searching questions concerning the reasons for the diagnosis of nephritis made upon patients that you were studying. These questions have shown that some of you are in a somewhat confused state of mind on the question of nephritis and the means at our command of differentiating the various types of the disease. One of you said to me a few days ago that the pathologists seemed never to see a normal kidney and, in a hospital of this kind given over chiefly to sick adults, it is indeed relatively rare for the pathologist to see a kidney that does not show the marks of disease or degeneration. Of course, not all of these individuals can be shown clinically to have renal impairment and only relatively few who have more advanced anatomic changes suffer from symptoms which could be traced to disease of the kidney. Then it must be evident that what we are seeking is not to detect absolutely the earliest morbid anatomic change, but to detect the early evidence of functional disorders, and, of course, these functional disorders must be supported in the last analysis by sufficient anatomic change to prove etiologic probability.

In the literature during the last few years so much attention has been devoted to the chemical aspects of renal disease that many of you have gained the impression, I find, that diagnosis rests purely upon the results of study of the blood and secretions. While these facts are always important and occasionally indis-

pensable, I am inclined to think that you assign to these methods an undue significance, sometimes to the neglect of other data. It is relatively true that the diagnosis of the more pronounced renal disorders can be made without these aids, and it is also true that occasionally we are apt to be led into mistakes if we depend exclusively upon functional tests, especially if only one or two tests be made.

In order to present to you concisely the problems which I wish to consider this morning we will begin with the case which you saw at autopsy yesterday. Will you kindly give a brief summary of that patient's clinical history.

CLINICAL CLERK.—Eugene H., age forty-five. (History No. 229,185.) This patient had been in the hospital a number of times. He was admitted first in 1903, and was operated upon at that time for inguinal hernia. According to his clinical record his heart was then normal and he was apparently in sound health, except for the hernia. He was discharged cured of the hernia. The next admission was in November, 1913, when he came to the hospital on account of dyspnea, palpitation, and pain in the left chest. At that time it was found that he had a very large heart and aortic insufficiency. The Wassermann test was taken three times, all tests being negative. He was again admitted a year later, in August, 1914, with the same symptoms, which were helped by rest. Again the Wassermann was negative. There were a number of subsequent admissions, in fact, one each year between 1915 and 1918 inclusive. There was nothing new in his record upon any of these admissions. In March, 1919 he came to the hospital on account of empyema in the left pleural cavity; was operated upon and apparently cured of this condition. He had no heart symptoms at this time, but it was noted that his liver was large. He appears to have been well until March, 1920, when there was a return of his old trouble, shortness of breath, palpitation, and some cough. Syphilis seems to have been constantly suspected, although the Wassermann tests were repeatedly negative; the only supporting evidence, other than the nature of his cardiac lesion, was the fact that his wife had had seven miscarriages.

The patient had been moderately alcoholic, having drunk considerable beer and whisky daily for a number of years.

The patient ceased work two months before the last admission to the hospital and had been in bed a good deal of the time for a month before admission. He stated that at times his ankles had been slightly swollen. Dyspnea had gradually increased until he had to sit upright in bed.

On examination, the principal signs worthy of note were his sallow, pale complexion; the dilated, pulsating veins in the neck; the very large size of the heart, the left border being 14 cm. to the left of the midsternal line in the fourth intercostal space; the loud diastolic murmur heard down the left sternal margin and a short, fainter systolic murmer at the apex. The pulse was of Corrigan type and was regular. There were râles at the bases of the lungs, indicating, probably, passive congestion. The abdomen was not tender, but the liver was large, easily palpable below the costal margin, and felt smooth. There was no fluid in the abdomen, nor was there any edema of the extremities. There was no enlargement of the lymph-nodes and the reflexes were normal.

The blood-pressure chart shows that his systolic blood-pressure ran between 120 and 140 mm. and his diastolic between 45 and 60 mm. His blood count indicated only a moderate degree of anemia of the secondary type. The non-protein nitrogen of the blood was 43 mg. per 100 c.c. The urine contained constantly a slight amount of albumin, but there were no casts until a few days before he died. The volume of the urine varied between 950 and 1400 c.c.; the night urine never over 600 and the specific gravity was between 1011 and 1020; in other words, there was pretty good concentration. Until the week before death the disease seemed to be a simple one of valvular heart disease, with chronic passive congestion accounting for the enlarged liver. There was a possibility of cirrhosis, which was discussed, on account of the alcoholic history. Albumin in the urine seemed to be adequately explained by the passive congestion of the viscera, but there was one fact which could not be explained adequately, namely, that there was a

small area of exudate in each retina; there were not, however, hemorrhages. This exudate appeared like that of nephritis. A few days prior to his death the patient began to have fever and the blood-culture showed pneumococcus. The complete clinical diagnosis, made before autopsy, is chronic valvular disease; aortic insufficiency; chronic passive congestion of all of the organs, more especially of the liver (possibly cirrhosis of the liver?); chronic nephritis, acute endocarditis, and bacteriemia.

DR. FOSTER: The organs from this case are of special interest. You see first that there is a very much enlarged heart and that the enlargement is due to hypertrophy—note the thickness of the left ventricle—and that there is also dilatation. There is considerable old involvement of the aortic valve, and then this fresh, greenish vegetation—the terminal superimposed pneumococcus infection—and observe the typical aortitis. The lungs show nothing remarkable, a moderate degree of passive congestion. The liver looks at first glance like a nutmeg liver, but there is also marked increase in fat and in connective tissue and the texture is notably hard on section; in other words, there is both passive congestion and cirrhosis. We are particularly interested, however, in the kidneys because, although you had heard the staff insist upon the probability of nephritis, it seemed to you that the diagnosis was made without due regard to the functional tests. You see at once that the kidneys are both considerably larger than normal and they do show some of those features which you are accustomed to associate with passive congestion, but, in addition, the capsule is adherent, the cortex is thinner than normal, and the kidney, as a whole, is notably granular and is resistant on section. A frozen section of this tissue presents all of the characteristic features that we are accustomed to associate with chronic nephritis.

Reviewing the completed record of this case, just what have we that would point to the possibility, or a probability, of renal involvement, in addition to the cardiac disorder? First, we have two possible etiologic factors, namely, syphilis and chronic passive congestion persisting over a long period of time. Either

one of these diseases alone, and certainly together, are very apt to result in degenerative changes in the kidney. Then, second, you recall the appearance of the man before his terminal infection had given its characteristic aspect. It was frequently remarked, you remember, that he looked like a nephritic, although there was very scant evidence of renal lesion. It is true that the non-protein nitrogen of the blood was slightly elevated and that the phthalein excretion was somewhat depressed, but both of these changes are occasionally notable when, apparently, the heart is entirely responsible. At best, the tests leave us somewhat in doubt of the proper interpretation to put upon the results. The single outstanding fact which points only to nephritis is the exudate in the retina, which we were assured could not be of luetic origin.

Interesting and complex as this case is, the most important feature about it is the clearness with which it illustrates the difficulty of differentiating the remote effects of cardiac disease from primary disease in organs—exemplified here in both kidney and liver. As a matter of fact it is impossible to think of renal function independent of cardiac and vascular phenomena.

The kidney differs from other secreting glands in its very intimate relation to the general circulation. No other gland responds so readily to changes in the blood flow and especially to blood-pressure, and none of the other glands ceases to secrete when the blood-pressure falls to a definite low level as in the case of the kidney. You recall that in the dog urine secretion ceases when the blood-pressure in the kidney falls below 30 mm. of mercury. The advocates of the filtration theory of the kidney function use this fact in support of their hypothesis because this amount of pressure just about neutralizes the osmotic tension of the blood.

There are apparently two main factors which determine the rate and the character of urinary secretion, namely, the mechanical factor, which is the influence of the general circulation, and, second, the chemical factor, meaning the composition of the blood. Our problem is made complex by the fact that of these two factors,

chemical and mechanical, one is seldom alone and dominant; changes in blood flow are so often, perhaps usually, accompanied also by some alteration in the chemical composition of the blood. In the type of circulatory disorder exemplified in this case we have the mechanical factor as nearly dominant as nature's experiments permit. You recall that in general urine secretion is dependent on both blood-pressure and on the velocity of blood flow. Rise in blood-pressure is accompanied by increase in urine flow, unless there be simultaneous vasoconstriction in the kidney, and a fall in blood-pressure is followed in general by a decreased urine flow unless the kidney vessels are dilated. The determining factor then is the capillary pressure in the glomerulus—not the general vascular pressure. Passive congestion of cardiac origin affects conditions which we can to some degree simulate by experiment. Goll, a pupil of Ludwig, noted the decrease in urine output following obstruction of the renal vein. This is an artificial passive congestion, and numerous experiments since Goll's have been done along these general lines, and they indicate that this type of stasis results in a lessened urine output, and the urine is concentrated and contains albumin and usually some blood. But have we not just accepted the principle that increase of blood-pressure in the glomerular capillaries induces increased urine flow, and it is evident that obstruction to flow in the renal vein will increase the capillary pressure within the kidney. Now, while obstruction of the vein does increase the capillary pressure in the glomerulus, the *blood-current* is at the same time slacker, and this decreased blood flow induces two results: a local asphyxia which injures the glomerulus, and second, a concentration of the blood constituents through water loss tending to a rise in the osmotic resistance to the secretion of fluid. There is then no inconsistency in the fact that passive congestion results in decreased urine, and it is readily comprehensible why all the urinary elements are likewise eliminated with difficulty. While the urine is concentrated and the percentage of nitrogen and salts may be up to normal, the total excretion for any period is deficient.

The next case that I wish to take up with you has some

resemblance to the case we have just discussed. Please give an abstract of the record.

Clinical Clerk: Sam. W. (No. 229,110). This patient has also been admitted to the hospital a number of times since 1915. His chief complaint is dyspnea on exertion. He has had in the past frequent attacks of sore throat, and chronic bronchitis intermittently for the last two years. He denies any venereal infection and has had no other diseases of significance. He works as a clerk and his habits are good. It was noted on his first admission, in 1915, that there was evidently mitral stenosis associated with considerable enlargement of the heart. He has been in this hospital six times in the last five years, and with each admission, following a period of rest in bed, his compensation has been regained so that he could resume work. Examination at the present time shows that the heart is considerably enlarged, the apex impulse being in the sixth space, 9½ cm. from the midsternal line. There is a presystolic thrill over the apex ending in a sharp tap and a loud presystolic murmur. The pulse has a typical bigeminal rhythm. There is some dulness at the right base posteriorly, which is due to fluid in the pleural cavity. The liver is markedly enlarged; is tender and pulsating. There is also some shifting dulness in the flanks and one sees that the legs are edematous. The blood-pressure is about 110 mm. systolic and 80 diastolic. The blood count is not significant. Of course there is considerable albumin in the urine and also hyaline casts.

Dr. Foster: The question we are now interested in is: Has this patient purely cardiac disease or has he also a significant nephritis?

The albuminuria and the presence of casts are as easily interpreted as evidences of cardiac lesion as of nephritis. This is also true of the edema of the lower extremities. We get no help from the ocular fundi, since these appear normal. The blood-pressure might be misleading had we not a long history and frequent observations in the past and recently, when the heart was perfectly compensated, up to last year, the blood-pressure always being within normal limits. The ability to secrete a

concentrated urine points usually toward a normal kidney, and in this instance the concentration has been constantly high, that is, above 1020 specific gravity. The ratio of the night and day urine is also normal; the night urine is below 600 cm., and the specimens, both of night and day, being of high concentration. This test cannot be used as an absolute criterion because occasionally one sees cases of exceedingly severe nephritis of the chronic type where the concentration does not follow the accustomed rule. Estimation of the chlorids in the urine or in the blood would not be of significant help in this case, since with edema of any cause whatever the chlorid excretion is abnormal. The phenolsulphonephthalein in several estimations had been slightly below 50 per cent. and the blood urea is above normal (urea, n. 33 mg.), but both of these disturbances are found in cases of severe cardiac decompensation. Summing up the evidence that we have available then, we notice that no single fact points exclusively to renal disease and that every sign is quite as well interpreted by the hypothesis of chronic passive congestion of cardiac origin as by nephritis. In other words, there is no evidence in the case to justify the diagnosis of nephritis, and we are sure of cardiac decompensation and some degree of passive congestion consequent to it. But conditions in cases of this sort are not always favorable to any certitude, as in this case where you have a long period of observation to aid you and a valvular lesion that cannot be interpreted erroneously. There is not now in the hospital a patient with the clinical picture we desire, but here is a clinical record of such a case. It is in some particulars similar to the case just seen.

The patient was a man fifty-two years of age, who came here because of dyspnea and swelling of his feet. His previous health had been excellent, so he stated, until a severe cold in 1918 kept him in bed about two weeks. Possibly this cold was influenza. Following this sickness he regained his strength very slowly, although he had no clear-cut symptoms other than fatigue. A month prior to his entrance to the hospital he noticed that his ankles were swollen, especially in the evening, though his shoes were not too tight in the morning. His

physician gave him some medicine and, since he did not improve, examined his urine. Probably albumin was found, as the patient was sent here with the diagnosis of acute nephritis. The patient was a rather stout man of good color and not apparently very sick. The notable facts recorded in his examination are rapid pulse with extrasystoles, slightly enlarged heart with a systolic murmur at the apex accompanying but not replacing the first sound; the blood-pressure was 120/75; some impairment of resonance at the base of the right lung with diminished breath sounds indicating a little fluid in the pleural cavity; considerable edema of the legs and feet. The first twenty-four-hour collection of urine measured 880 c.c., specific gravity 1024; albumin +; hyaline and granular casts were both present. The phenolsulphonephthalein test was 30 per cent. for two hours.

With this data gathered at your first examination you would not be quite clear in your mind about the diagnosis and you would consider presumably several possibilities, the order depending on your individual mental bias. Considering his age and the origin of his symptoms in an infection, one thinks of myocarditis and cardiac dilatation; his habitus and albuminuria and the infection again suggest nephritis; or again, he may have had a high blood-pressure for some time and, on that account possibly a poor myocardium, which was further damaged by the infection. How do you think you would approach the problem, Mr. X?

Clinical Clerk: Of course I am not sure what I might have thought, but the irregular pulse impresses me now more than the albuminuria. At any rate, one would be right in insisting on absolute rest for a period and, if the pulse-rate did not decrease, I should try digitalis. Further tests could then be done.

Dr. Foster: You are quite correct in considering your problem first as a therapeutic one. This patient was, of course, kept in bed. Now, to resume his record, the ocular fundi were normal and the absence of retinal edema is significant; all the usual procedures in the way of tests were indecisive in result. We were then doing many concentration tests on urines and some of these suggested a fixation of concentration, while some

did not. Gradually this patient improved, the edema subsided, and the murmur at the apex was just audible, a trace of albumin, however, persisted in the urine. There was never an abnormal amount of night urine and by no method could nitrogen retention be detected. Finally, when the patient was well on in his convalescence apparently and there was no detectable edema, he received 10 grams of sodium chlorid for two days in excess of the salt taken in his food. He developed considerable thirst in consequence and passed more urine than usual, but the significant fact to us was that he gained just under 2 pounds in three days and promptly lost it again. Of course, all due attention was given to possible mistake in the causation of this gain in weight, constipation, for example. The case, in brief, was one of cardiac disorder, but also he had a very early or slight renal involvement, which might easily have been overlooked. This case illustrates a principle which we use constantly in diagnosis, namely, in order to detect early impairment of function it is necessary to impose strain. In the case under consideration the kidney was able apparently to meet the usual demands so nearly that no evidence of stress appeared until unusual conditions arose. But I do not wish you to get the idea that refinements in diagnosis of this sort are purely for the satisfaction of an academic standard. These attempts may at times seem of that character, but their object is first and constantly to enable us to treat these diseases more effectively. If you can recognize a confusing syndrome as due to a cardiac disorder you are in a position to give effective help—otherwise you are not. In pure research even that is the object, though the road must often be indirect.

The next case bears some resemblance to the last in some of the clinical signs, and we will take this patient next.

Clinical Clerk: Abstract of record: Abe G., aged sixteen. (History No. 228617.) The patient has always had good health and has had no serious sickness. He was in the Navy during the war, acting as machinist, and was given his discharge in January of this year. In February he contracted a cold which confined him to the house for five days; then he returned to his work. A few days later he noticed that his face was swollen around the

eyes and a week or so after this the patient noticed that his body was swollen. He said that at this time he was slightly short of breath and had a little headache. He did not notice any change in his urination or in the color of the urine. For a few days before admission to the hospital he suffered from persistent headache. There had been no visual disturbances, no epistaxis, no nocturia. Upon examination on admission the patient appeared very ill, but said that he was not uncomfortable. The eyelids and face were distinctly edematous. The significant facts brought out by the examination were that the heart was not apparently enlarged and there was no evidence of valvular disease. Some impairment of resonance at the bases of the lungs posteriorly along with diminished breath sounds and voice conduction indicated fluid in both pleural cavities. The abdomen was distended with fluid, tense, but not sensitive. There was also considerable edema of the thighs and legs.

In the absence of any sign indicative of cardiac disease the general anasarca seems probably of renal origin. The twenty-four-hour specimen of urine measured 980 c.c. and the specific gravity was 1031. There was a very large amount of albumin; both hyaline and granular casts, a few leukocytes and red blood-cells. The blood count showed secondary anemia and the Wassermann test was negative. Examination of the fundus of the eyes revealed considerable edema, but no hemorrhages or exudate, and the blood-vessels did not appear abnormal.

Dr. Foster: In this type of nephritis it is not usual to find exudate or hemorrhages in the retina. It is, however, quite common to find varying degrees of edema. There seems no question about the diagnosis of nephritis in this case. The only question which we have to settle is the type of renal disease. Is this, as it would seem to be, an acute nephritis, following some infection which the patient called a "cold," or have we to deal with an acute process superimposed upon a chronic, latent condition? We have to remember that this patient was sick for a number of weeks before he came under our observation. In order to determine the questions we have asked it will be necessary to resort to some special tests. In the first place, while

the ophthalmologic examination is not conclusive, the absence of hemorrhages and exudate suggests that any chronic process has not been of long duration. Retinal changes are very apt

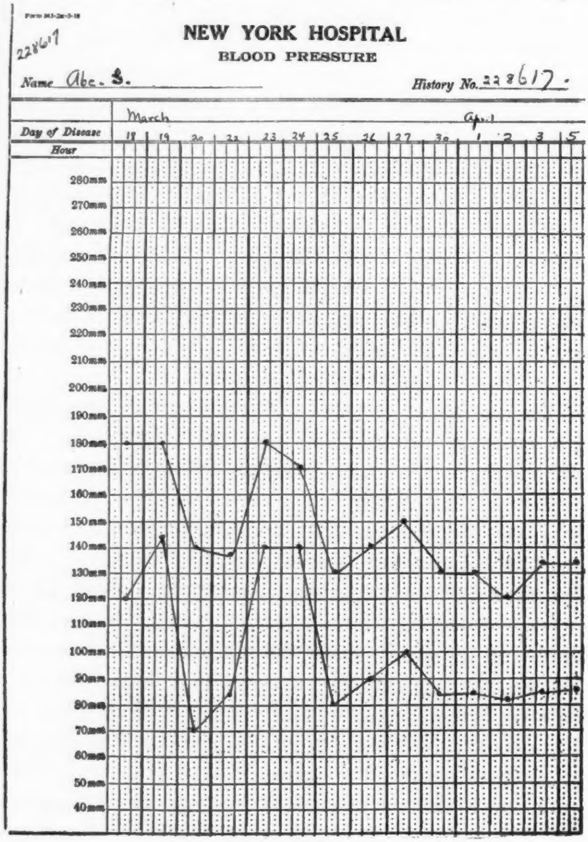

Fig. 1.

to occur, in fact, are of much more frequent occurrence than usually stated, because this type of examination is often omitted.

The blood-pressure chart, which I show you, does not give us definite evidence of the type, since transitory rises in blood-pres-

sure similar to those depicted in this chart are often seen with acute glomerular nephritis—that of scarlet fever, for example. The phenolsulphonephthalein is suggestive. The first estimation was 40 per cent.; the second estimation, two weeks later, was 30 per cent. So far as this test would indicate the disease process is progressing unfavorably. Have we any confirmatory signs pointing in the same direction? The first estimation of non-protein nitrogen was 56 mg. per 100 c.c. of the blood. The second estimation was 61 mg.; the third, 64; the fourth, 88 mg. In brief, there is a constant increase, during the period of observation, in the amount of waste nitrogen in the blood, and this in spite of the fact that the patient has been on a low protein diet during this period. Incidentally, I might mention that the diet has not been intentionally scanty, but because the patient has not had an appetite to take more than a very small amount of food. During this same period the amount of uric acid in the blood has risen from a normal figure to one that is distinctly abnormal. I shall refer to that somewhat later.

So then, you see, that while the patient has been under observation he has developed a pronounced nitrogen retention or, as the French say, azotemia. Moderate degrees of nitrogen retention do occur with cardiac decompensation, as already mentioned, but hardly to the degree manifested in this patient, and, moreover, there are not any symptoms of decompensation nor any signs of valvular or myocardial disease. The most reasonable explanation to be offered in this case is that the initial infection, which the patient termed a cold, was followed by an acute nephritis. This acute nephritis, instead of subsiding, the inflammation has continued and, as you know, all long-standing inflammations are accompanied by connective-tissue proliferation. This process in the kidney gives rise to that picture which morbid anatomists are accustomed to speak of as secondarily contracting kidney or, in a terminology I shall explain later, subacute glomerular nephritis. Functionally this condition makes itself manifest in just those signs that we observe in this patient. If it were not for the very considerable nitrogen retention we should doubtless regard this case as one of paren-

chymatous nephritis, or the type that is spoken of nowadays as nephrosis. Anatomically the kidney in these cases more closely resembles parenchymatous nephritis than the contracted kidney of chronic interstitial nephritis, but there is this difference, that the kidney's substance is firm and harder, and microscopic examination reveals a proliferation of the interstitial tissue and not infrequently the obliteration of glomeruli and tubules.

Had the opportunity come to us to study this case at an earlier period in the disease we might have regarded it correctly as an acute nephritis of the glomerular type. By that you are not to understand that the glomerulus is the only element in the kidney that is diseased in typical glomerular nephritis, of scarlet fever, let us say, but rather the element where disease is most conspicuous. You recall that several years ago interest was reawakened in the endeavor to make a finer classification of diseases of the kidney, to differentiate, for example, disease of the glomerulus from that of the tubule; to distinguish a primary disorder of the blood-vessel from the renal element, and Schlayer's name was particularly associated with these studies.

Various classifications of renal disease based upon histologic changes are known to you, for example, glomerular nephritis, tubular nephritis, etc., and numerous attempts have been made to produce these isolated lesions experimentally, and from that to build up a more refined diagnostic procedure than we now possess. The studies and conclusions of Schlayer were most pretentious in their object and were based on the idea that some poisons, for example, arsenic, act on the glomerulus, while other poisons, such as uranium, induces lesions chiefly in the tubule. But these investigations of Schlayer's produced little if anything of permanent value, because it has been shown that none of the poisons known is exclusively "vascular" or "tubular"; indeed, they are not even exclusively renal in their effects. In brief, the function tests, such as the lactose and iodid tests, which resulted from Schlayer's work are quite abandoned, and these laborious researches establish that we cannot at present bring histologic lesions in the kidney into direct relation with functional behavior. It has been very prettily shown by Whipple in his

study of the effects of toxic proteose that severe disturbances of function (low phthalein excretion and nitrogen retention) can occur without any significant or detectable alteration in the renal cells.

It is necessary that we consider our problem of disease in the patient and in general from a broad point of view. Disease of the kidneys is seldom if ever unaccompanied by general disturbances, and this must not be overlooked. For, granting a definite lesion, the important question is its cause. A more promising field for study than the one above outlined would seem to be a consideration of the chemical factors of renal secretion; the influence of variations in the blood plasma on the flow and composition of the urine; and quantitative estimations of elements in blood and urine would appear a sounder basis of classification. The degree of the renal lesion would then be measured by the ability of the kidney to meet alteration in blood plasma by changes in the urine composition.

Reference should be made in passing to the classification of nephritis which has been suggested by Vollhard and Fahr. You will best orient yourself in this classification by recalling that the old term of "parenchymatous nephritis" encompasses both the tubular nephritis and acute glomerular nephritis of Vollhard and Fahr. According to these authorities, tubular nephritis is characterized clinically by edema and a scanty urine of high specific gravity containing much albumin. There is practically always a low blood-pressure. Tubular nephritis, or nephrosis, shows little or no tendency to develop uremia and, in a general way, the prognosis is good. With acute glomerular nephritis, on the other hand, while there are many symptoms in common, such as edema, oliguria, the blood-pressure is usually elevated and there is a decided tendency to uremia. Glomerular nephritis occurs also in the chronic form, which in the beginning may be very insidious in its manifestations. These cases are usually recognized by their peculiar pallor and emaciation, the frequency of digestive and circulatory disturbances, and the high blood-pressure and cardiac hypertrophy. The urine is increased in amount and there is nocturnal frequency. These patients are

apt to have albuminuric retinitis. Dropsy is infrequent and uremia a common termination.

Under "renal sclerosis" Vollhard and Fahr grouped the final renal changes resulting primarily from fibrosis, for example, the sclerosis following glomerular nephritis and that resultant upon arteriosclerosis.

While this anatomic division is probably an advance upon those heretofore used, it has the same defect inherent in all classifications of renal disease. First, we very seldom see a diseased kidney wherein one element, such as the glomerulus, is involved, the tubule being quite normal. As a rule all elements are involved and any question of degree resolves itself into a matter of opinion. Then, too, it is assumed in these classifications that we can estimate from the appearance of a cell the probable degree of impairment of its function during life—relatively a dangerous assumption. In the third place, by connecting a lesion in a renal element, such as tubule or glomerulus, with specific symptoms, for example, edema, we are assuming a knowledge of physiology which we certainly do not possess.

Of the making of classifications of disease, like books, there is no end, and new classifications are of use in stimulating investigation in these diseases. They are helpful too as we approach constantly more closely to the position which is the test of science; the ability to predict—prognosis. But classifications based purely on anatomic changes in an organ whose physiology is quite obscure helps therapeutically not at all. Today there is no consensus of opinion even among physiologists as to the specific function of the glomerulus or the tubule. We speak of the kidney as a secreting organ and mean that the cells abstract from the blood materials discharged into the tubules, but *which* cells secrete urea and which salts? The advocates of the filtration doctrine hold a very different idea, and assign to the tubular cells a function of resorbing the excess of water discharged by the glomerulus. In such a clouded state of knowledge, of what practical gain is it to classify a case of nephritis as glomerular or tubular? Little enough are we able to accomplish at best, but a physiologic point of view is of some assistance, and, for that

reason, in this clinic we are accustomed to emphasize the disordered physiologic function in renal disease rather than the anatomic lesion. We have then nephritis with defect of water and salt elimination and nephritis with defect of nitrogen elimination and mixed types, where both of these functions are disordered. The last case you saw was of this mixed type. Early in the disease the retention was, possibly, exclusively of salt and water. Some of these cases respond in a gratifying way to diets poor in salt. Epstein has found that some cases do well on high protein diets. And, unfortunately, I must add there are many not benefited by any mode of treatment, but progress only downward; the early salt and water retention being complicated later by nitrogen retention. Such cases often terminate in uremia if they escape infections.

We must consider next nitrogen retention since it is the notable disturbance in many cases of nephritis. An increase of urea in the body fluids in nephritis was, you recall, detected by Bright in his classic studies. The development in technical methods has stimulated and aided clinical study wonderfully during the last decade. Attention, of course, was focused on the nitrogen bodies excreted in the urine, and it has been found that there is some relation between the severity of the renal disease and the substance excreted. Creatinin, for example, is retained in the blood only when the disease is far advanced, while uric acid retention may occur without symptoms. Urea retention occupies apparently a mid-position and because of the ease of technic it is the substance commonly estimated in blood.

The next patient represents a classical type of the disease we are studying. Will you please give the history of this patient?

Clinical Clerk: This patient, Gaetano A., is forty years of age (history No. 229,582). He came to the hospital complaining of shortness of breath and weakness. There is no history of any disease in his family, so far as he knows. He has never had a serious illness. There has been some trouble with his nose, which he describes as "catarrh," marked by symptoms of obstruction to breathing. This difficulty is of very long standing. He has not had headaches, but he states, on direct questioning,

that his eyes have been poor for the last three years. There have been no pulmonary symptoms nor any gastro-intestinal disturbances. He gives a history of lues twenty years ago and for this he received a long period of treatment. He says that he has had frequent urination, especially at night, for the last seven or eight years, and for about the same length of time he has had cramps in the calf muscles. This pain he describes as "gripping," says that it starts in the calf of the leg and travels up to the hip. Occasionally similar pains occur in the arms. The chief symptom at present, shortness of breath, began indefinitely about six months ago, and during this time he worked only two oı three days a week. Apparently there was increasing weakness as well as dyspnea and occasionally slight swelling of his feet. None of these symptoms, with the exception of the dyspnea, have increased in severity. There have been no headaches, no nausea, or diarrhea. His eyesight is not worse than it has been. The dyspnea, however, has increased and for the two weeks prior to admission the patient had difficulty in sleeping on account of it.

On examination one is struck first by his pasty complexion. There is perhaps a suggestion of edema under the eyes. Atrophic rhinitis explains the catarrhal symptoms he has complained of. The retinal examination showed many hemorrhages, some patches of exudate and degeneration, and also sclerotic arteries, a typical picture of albuminuric retinitis. The heart is appreciably hypertrophied, without any evidence of insufficiency, and the blood-pressure on admission was 220 systolic and 160 diastolic. The Wassermann test is negative. In other respects the examination revealed nothing significant.

The urine is of low specific gravity, contains albumin in some specimens, not in all, and there are a few hyaline casts. The phenolsulphonephthalein excretion was too slight for measurement. The blood urea n. was 152 mg. and the blood sugar 214 mg. per 100 c.c.

Dr. Foster: How do you interprete your data in this case?

Clinical Clerk: The case is one of advanced nephritis of the nitrogen retention type.

Dr. Foster: What facts are to you most important in establishing your diagnosis?

Clinical Clerk: The history is not as conclusive as one might have expected, considering the severity of the disorder. The diagnosis rests chiefly upon the physical signs, that is, the albuminuric retinitis, the high blood-pressure, the persistent low concentration of the urine, and the very high blood-urea.

Dr. Foster: Notice the general appearance of this patient; he looks sick, his skin is pallid; he is undernourished and anemic. This aspect is not unlike that of a case of phthisis; you can understand why one of the diseases most frequently mistaken for pulmonary tuberculosis is chronic nephritis. Chronic bronchitis is often a complication of renal disease and completes the resemblance. Why do you say that the disease is advanced?

Clinical Clerk: Estimations of the creatinin of the blood have been made and this is now about 10 milligrams, three times the normal figures.

Dr. Foster: This case represents the text-book variety of chronic nephritis, probably of considerable duration. No disease can be more insidious, and even yet he has not developed the symptoms we associate with intoxication, notably headache and nausea. But I wish to call your attention to the fact that there are already uremic manifestations and, while he seems apathetic, he is restless and irritable. Mentally he is far from lucid, his answers are slow, evidently uncertain, and, while he is not now disoriented, the strain is apparent, and at times he is delirious. There is, in brief, a mild toxic psychosis. There was the possibility of complicating cerebrospinal syphilis which we believe to have excluded. In that relation, let me remind you that the colloid gold curve of cerebrospinal fluid in uremia may fall within the syphilitic zone. Have you no explanation to offer for his slight fever, which I notice runs between 100° and 101° F., and also the considerable leukocytosis of 22,000?[1]

Clinical Clerk: I know that every effort has been made to exclude any infection; the sinuses have been examined and the

[1] This patient died three weeks later following uremic convulsions.

teeth, and there are no signs of any inflammatory process anywhere so far as can be discovered.

Dr. Foster: You will observe that the majority of cases of uremia developing as an outcome of this type of nephritis have fever and leukocytosis. The explanation of this is not entirely clear, and I have wondered if the fever were possibly like the xanthin fever of which perhaps you have heard, or in some cases it may be desiccation fever. It is conceivable that the leukocyte increase might be due to a similar cause. Whatever the cause, fever and leukocytosis are common in uremia of this type. On what principle do you treat this patient?

Clinical Clerk: It was very evident that his nitrogen metabolism is defective, and that he cannot excrete the waste products. The indications would be then to reduce the protein ingest to the lowest possible terms, and this was effected by giving him a carbohydrate diet. Of course in addition he had the routine rest in bed and was encouraged to take as much water as possible. On the first day of his treatment he received several intravenous infusions of glucose.

Dr. Foster: What diet would you employ to secure a minimum protein ration?

Clinical Clerk: The ideal food-element would be glucose on account of its effect in sparing protein catabolism of the body tissues, and, in fact, that was the chief food for two days. It was used in beverages, intravenously in 10 per cent. solution, and by the Murphy-drip method. When solid food was given we used rice, sugar, stewed fruits, and cream. Later we can use milk for a graduated increase of protein, and butter to supply calories. Rice is a large element in the diet because it is poor in protein.

Dr. Foster: You mentioned that you encouraged the patient to drink copiously and, you also used other means to supply fluids. That is important, and, we think, founded on a sound principle. We noted in this clinic that when patients with nephritis and nitrogen retention were given weighed and analyzed diets so that we knew exactly the nitrogen intake, the nitrogen excreted in the urine then depended largely on the amount of water the

patient drank—provided the water is excreted and the urine volume increases. We speak of fixation of concentration of the urinary nitrogen, meaning that the patient is unable to secrete urine containing the normal 2 to 2.5 per cent. of nitrogen, but at best perhaps only 0.5 per cent. Evidently then the total nitrogen eliminated bears a relation to urine volume. We found that utilizing this principle combined with reduction in the protein of food we could in some cases reduce the blood-nitrogen to a figure approximately normal and that the patients recovered some semblance of health. Not always can one succeed however. The obstacles are: (*a*) failure of water diuresis, edema resulting, (*b*) cardiac embarrassment due to the extra work, (*c*) fixation of nitrogen at a percentage so low that an adequate water intake is impossible to accomplish. The next case to be presented was treated here over a year ago with some success.

It is said a good physician is notable for what he does not do—beware of diuretic drugs.

We have had an opportunity of observing this patient over a considerable period of time. Will you please read a summary of her clinical record.

Clinical Clerk: This patient, Tillie S., is thirty years old and she was admitted on the 13th of April, complaining of pain of the lower part of the abdomen. Her family history is not important. She has always been well and remembers no sickness of any kind. She says that she has had nocturia once or twice a night all her life. Several years ago she consulted an oculist on account of blurring of her vision. We do not know what disturbance was found, but she was given glasses. The latter part of 1918 she began to have violent headaches and gave up her work. These headaches were associated with attacks of vertigo. Several days before her first admission to the hospital, in January, 1919, she was very much depressed mentally and had considerable nausea. Her friends state that shortly after this she became mentally "hazy" and they also state that she had five convulsive seizures, and then she was brought to the hospital. At the time of her first admission the following facts were brought out: There was an area of retinal sclerosis in the left eye marking the

site of an old hemorrhage. The blood-pressure varied between 190 and 220 systolic and 130 and 150 diastolic, and the heart was somewhat enlarged, but there were no signs of valvular disease. She had a slight fever for the first few days at that admission. The urine contained albumin and casts, the daily volume varying between 800 and 1500 c.c. The concentration tests at that time indicated considerable adaptability in the kidney, as the accompanying chart shows, nor was there any marked disturbance in chlorid excretion. The nitrogen excretion, however, was defective. It was interesting also that the day urine was 1038 c.c. and night urine only 440 c.c. as a maximum. The phenolsulphonephthalein estimations were made a number of times, the highest being 14 per cent. for two hours. Also estimations of non-protein nitrogen were made, the highest being 107 mg., which gradually fell to 65 mg. before the first discharge from the hospital. The creatinin of the blood was constantly about 4 mg. This patient had several convulsive seizures at the time of the first admission and she was discharged with no expectation that she would recover health. Since the discharge from the hospital she has lived at home and has been, for the most part, fairly comfortable except for periodic headaches, which she says were of agonizing severity. The patient has, however, apparently been rather weak and lacking in energy, since she states that she has done very little and has not been able to help in domestic duties. For the last six weeks prior to the present admission the headaches have increased in frequency and it is on account of them that she has been compelled to return to the hospital. On examination the patient does not now appear seriously ill. She is well nourished, even somewhat too stout. There is no evidence of cardiac embarrassment, although the blood-pressure is exceedingly high—at present the systolic is 220 mm. The heart is definitely enlarged. There are no murmurs and no arhythmia. The lungs and abdomen apparently are normal. There is no edema of the extremities, no tenderness over the nerve trunks. Examination of the ocular fundi shows a moderate degree of optic neuritis and some new patches of exudate on the temporal side of the disks of both eyes. The

vessels in the retina are remarkably tortuous. The concentration test for nitrogen was done twice and, although there is a marked increase in the non-protein nitrogen of the blood, the nitrogen excretion for twenty-four hours was only 2.87 grams, which with the urine volume of 1100 c.c. works out to a concentration of 0.26 per cent. The specific gravity of the urine, however, runs as high as 1020. Evidently the concentration is defective in respect to nitrogen only. The other tests confirm those of the earlier admission and are not in any essential different from them.

Dr. Foster: What then is your diagnosis in this case?

Clinical Clerk: It is a case of chronic nephritis or, in the terminology used in this hospital, chronic nephritis with nitrogen retention.

Dr. Foster: Do you think that you could have arrived at this diagnosis without the laboratory aids which you have made use of?

Clinical Clerk: I am not so sure that the case would have been as clear to me as it now is, but there are some outstanding features which I should think would have pointed only to the diagnosis. The most impressive of these are the symptoms: headache, nausea and vomiting, and convulsive seizures, preceding the first admission and the high blood-pressure and exudate in the retinæ. The routine laboratory examination of the urine are perhaps suggestive, but are not so important as the other clinical manifestation already mentioned.

Dr. Foster: Of what especial use then do you think the laboratory procedures have been, other than satisfying your curiosity concerning the metabolism and perhaps giving you some added facts of a confirmatory nature?

Clinical Clerk: The laboratory results have been of the greatest help in indicating the line of treatment that should be pursued for the benefit of the patient. But I do not think the severity of the nephritis would have been appreciated without these tests, the patient looks too well.

Dr. Foster: You stated also that there is now an optic neuritis of low grade. There may be no confusion here because

the other retinal lesions are so typical, but we have to remember that in some rapidly developing cases optic neuritis exists alone and then in association with headache and vomiting the resemblance to brain tumor is evident. One easily appreciates how slovenly made examinations may lead to a grave error and irreparable injury.

Not in every instance are all signs and symptoms so definite as in this case. Let me take the functional tests first, since on them you have focussed your attention. While nitrogen retention is generally detectable in nephritis without edema, yet not invariably, even cases of uremia may fail to show the increase. Other cases have remarkably high phenolsulphonephthalein excretion, but with other evidences of advanced disease. The nitrogen concentration in the urine and the total elimination under rigid control may be, for short periods, so satisfactory that it deceives the unwary. The lesson to us in this is: Do not depend on any one test, and regard no single observation as final. Your minds now being "polarized," as Oliver Wendell Holmes said, nausea, vomiting, headache, and convulsions suggest only nephritis and the uremic syndrome, but suppose you saw for the first time a child who had had these symptoms a week and was stuporous. These are the symptoms of onset of many infections. Fever is not a differentiating fact, since it is common in "dry" uremia. Chronic nephritis is not rare in childhood, and the problem I have outlined for you may be difficult indeed. Mistakes are commonly of two sources: overlooking a sign, ignoring a fact.

Reference must be made in passing to some functional tests not a part of the routine in this clinic, and the Ambard quotient is of this class. Several years ago rather high hopes were entertained of the help to be derived from this test, but it seems the promise was not fulfilled, since the test is largely abandoned. Advocates of the test claimed for it chiefly data bearing on prognosis, but current opinion apparently regards the formula as confirmatory only of the obvious. Now while it is doubtful whether the action of the living kidney can be circumscribed within the bounds of a mathematical formula, yet the principle

involved, it seems to us, was correct in that the rate of excretion by the kidney was qualified by consideration of the excretory product in the blood during the period of observation. In some excellent studies on the excretion of urea in experimental nephritis Addis and his associates have observed that the nearest approach of co-relation between functional and anatomic change can be secured by considering together the amount of urea excreted during an hour period and the blood urea at the same time. When the anatomic lesion in the kidney is slight, in order to reveal functional change it is requisite to create artificial conditions, that is, to impose strain by administering considerable doses of urea. There is not yet any sufficient volume of clinical data on this test, but the principles involved, namely, imposed strain, and the relation of blood concentration of the substance to the amount excreted during a test period, are correct. The formula is thus expressed: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. blood (mid-hour)}}$. It is also interesting that neither the blood concentration alone nor urine concentration alone revealed adequate relation of function to early structural change. This fact has a practical bearing on tests of concentration in common use and warns us against too nice distinctions. Our interpretations of percentages of blood-urea, for example, or urine concentrations are justified only when there is a marked deviation from normal ranges. The next case presents a different picture.

Clinical Clerk: Nora M. (history No. 227,179). Forty-seven years old; came to the hospital on account of palpitation of the heart, shortness of breath, weakness and swelling of ankles. The family history is in doubt. The patient states that she recalls no serious sickness until six years ago she was operated upon in this hospital for a fibroid tumor of the uterus. For an indefinite period after this she was in good health, but for a couple of years, perhaps longer, she has had dyspnea on exertion. This symptom was not of serious embarrassment until last year. Before her second admission to the hospital, in January, 1920, she had some headaches, but was troubled chiefly on account of the palpitation. About this time she took "cold" and all the

symptoms became more severe and she was too weak to work, and at this time there also developed a slight swelling of the ankles. There has been no disturbance of vision, no edema of face, no gastro-intestinal symptoms, no polyuria or frequency.

The salient facts determined at the admission in January were obesity, cardiac hypertrophy, and dilatation; normal cardiac rhythm; hypertension, systolic pressure 180 mm., diastolic 130 mm.; slight edema of the legs. The urine was concentrated and contained albumin and casts. Repeated tests of the renal function were essentially normal in result. For example, the phenolsulphonephthalein test was 52 per cent. and the blood-urea 22 mg. All the various tests were done and gave comparable results. The retinæ were normal except that the arteries were tortuous and veins compressed. The diagnosis determined upon at that time was primary hypertension, cardiac hypertrophy, myocarditis, cardiac dilatation, passive congestion of the lungs and kidneys. She was treated by rest in bed, Karell diet and digitalis, and gradually improved, so that she left the hospital free of symptoms. The blood-pressure remained high, however, and not changed by any procedure tried. After discharge the patient was comfortable for about six weeks. Gradually dyspnea developed and finally orthopnea, and she returned to the hospital last month with marked edema of the legs and fluid in the right pleural cavity. It was increasingly difficult to keep the patient comfortable, and on account of the blood-pressure, which was now constantly over 200 mm., no measure to relieve the heart strain was successful. She was bled several times. Finally a cerebral hemorrhage occurred during sleep, resulting in complete right hemiplegia.[1]

DR. FOSTER: What is your diagnosis?

CLINICAL CLERK: The special tests for nephritis have been done a number of times and there was no evidence of impaired renal function. I presume the case should be classified as one of essential hypertension with terminal cerebral hemorrhage.

DR. FOSTER: Do you, however, believe, all things considered, that the kidneys are anatomically normal?

[1] She did not recover consciousness and died in forty-eight hours.

Clinical Clerk: That is very doubtful. But in managing the case we did not need to consider her chief danger from defective secretion, but rather from cardiac disorder or cerebral accident.

Dr. Foster: This term "essential or primary hypertension" was first coined because it was found that an occasional case of high blood-pressure showed at autopsy only insignificant disease of the kidneys. There are undoubtedly such cases, but they are uncommon, and even then you understand the latitude allowed the pathologist in deciding what is normal. Now a transition in thought seems to be taking place in that some regard essential hypertension as the primary disorder and nephritis a sequal. In a sphere of medicine where we have so few facts it seems unfortumate to use terms which aim at definite conclusions. The symptomatology of nephritis is quite varied and, for all that is known to the contrary, it is quite as likely that hypertension may often be the only manifestation for considerable periods as that hypertension causes renal degeneration. We have in these diseases a profound metabolic disturbance manifested sometimes chiefly as hypertension, again as frank nephritis, and in otber cases as arterial sclerosis. It is premature to hold opinion as to which is cause, which effect. These are subjects for research, not for idle dogmatic statement. The facts indicate in general only relative differences. Excluding the accident of intercurrent infection, nephritis tends to terminate in an intoxication, uremia, but many cases succumb to cardiac degeneration or cerebral accidents; while hypertension tends to cardiac disorder and cerebral hemorrhage, but some cases end in uremia.

In the absence of a clear understanding of the primary cause we are forced to regard these disorders as syndromes and endeavor to aid as best we may some one failing function, or if we can, to postpone the failure. In practice that is our aim; so to arrange the patient's mode of life and habits that less strain will fall upon an overtaxed heart or a cerebral vessel. In general that means to correct every single possible cause of abnormal strain on the patient's vitality. Food, rest, work, foci of infections, exercise—all must be considered—remembering that these patients are

fundamentally disordered and react excessively to the effects of various stimulations and depresssion. Because remarkable benefit occasionally results from a sharp reduction in food or the removal of an infected focus these have been assigned a causal relation to hypertension. Few disorders are distinguished by so many immediate causes!

As you are quite well aware, the causation of the increased blood-pressure in essential hypertension is unknown. There are many opinions, but little evidence in support of any of them. Now one of the observations that has been often made on the blood in these cases is that the total solids, and particularly the proteins, are considerably elevated above normal. This condition would have the effect of increasing osmotic resistance to secretion and hence a fall in urine secretion. In order to maintain the normal urine flow a compensating factor for this osmotic resistance must enter, and the usual compensatory factor is a rise in the blood-pressure. This is purely conjecture, but it is a problem worth a little study. Then, too, blood colloids, like colloids in general, form combinations with water in various proportions (analogous to water of crystallization) and these combinations are quite sensitive to many influences—hydrogen concentration, salts in solution, etc. So that in the field of hypotheses there are ample problems for solution, and we need not fall back on the rather clumsy mechanical conceptions that have been offered to explain essential hypertension. The causal factor may be as simple as some conceive, but probability is against it.

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CLINIC OF DR. HARLOW BROOKS

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THE COMPLICATIONS AND SEQUELÆ OF INFLUENZA AND THEIR MANAGEMENT

A LITTLE over a year and a half ago I was permitted to analyze and study a group of nearly 9000 fatal cases of supposed influenza. The most striking and outstanding fact which this study presented to me was that in but very few of these instances could the immediate cause of death be attributed to the infection itself, but rather to some complication or sequence of it. Many of these cases had been very hurriedly and perhaps superficially studied, it is true; they had been collected and reported by a great many different physicians in the stress and excitement of war, and in many instances were records made while actually under fire. However, I do not think in all the world there could have been selected a more virile, able, and conscientious body of medical men. The fact that they were where they were is ample index of that, and the fact that their conclusions, in the main, corroborate those of the practitioner in civil life makes this review of particular importance because of the very large amount of diversified material which it represents. All of these cases were studied at autopsy, and while in some instances the investigations were not elaborately detailed or highly scientific, their general bearing is quite conclusive in my opinion. Of this group of fatal cases which were collected from the entire American Expeditionary Forces, just 2 were reported as dying of "influenza." Some cases were recorded as dying of mastoiditis, complicating influenza, some of general septicemia terminating influenza, and most of all, naturally, as dying of a bronchopneumonia terminating an influenza. The essential point was

that none of these medical officers were content with a diagnosis of "influenza" as sufficing for a cause of death. In this viewpoint I think that most Boards of Health would entirely coincide, and very few would accept as a sufficient cause of death the sole diagnosis of "influenza."

As a matter of real clinical fact the disease of influenza is chiefly characterized by its complications rather than by its own specific picture. Divest even its onset of the typical symptoms of those secondary conditions which occur in the disease and the diagnosis of "influenza" would be a very difficult one to make, and can be arrived at only by exclusion, unless one is content to accept as conclusive the presence or absence of the Pfeiffer bacillus.

We are still much in the dark as to the cause and nature of influenza; few of us now accept the influenza bacillus, even after Cecil's very striking demonstrations. None of us, I fancy, thinks for a moment that the pneumococcus, the Streptococcus hemolyticus, or the viridans is the essential etiologic agent, and yet we must confess that, in so far as our present knowledge goes, it is these secondarily infecting organisms which mostly cause the complications which mark the disease and which eventually kill the patient in nearly all instances.

From the standpoint of treatment the same curious anomaly pertains. Within a few days after the onset we are no longer concerned with the "influenza," but with the pneumonia, the mastoiditis, the neuritis, the myocardial degenerations, or perhaps the intense asthenia which are the results of and not the disease itself.

Still another peculiarity of this infection is this: these complications which make up, as we have seen, the dominant part of the infection, in so far as the therapeutist is concerned, need not occur immediately after the onset of the disease; in fact, they are more frequent after the patient has been up and about from his original infection—they may even occur weeks after the acute onset of the "influenza"; neither are the severity and the gravity of the sequelæ in any way a measure of the gravity, or even the character of the disease from which they are supposed to originate.

Are they in reality influenzal in origin, or are they entirely independent of the original infection, and in only the most remote way possible connected with the primary disease? Do they appear with this great frequency and with so great a similarity in character and course after influenza solely because the body resistance is broken down by the original and perhaps independent infection and thus rendered susceptible to secondary infections?

These are matters of very great importance and questions which we must answer in a much more definite and satisfactory way than is now entirely possible before we can expect to gain a better mastery over this infection and its multitudinous complications.

Of very direct bearing on the question is that of the degree of lowering of body resistance as a result of the specific infection of influenza. I am quite sure that no division of opinion among clinicians of experience can exist on this point. The post-influenzal subject is far more susceptible to a typhoid infection, to a gangrene or gas bacillus infection, after a lacerating wound to a delayed union in a fracture than a perfectly normal person, and certainly in these conditions mentioned rather at random no question of a specific toxemia contributing materially can be admitted, or at most insisted upon.

Still another viewpoint is possible to explain such conditions as the bronchitis, bronchopneumonia, myocardial degeneration, myositis, etc., that occur with so very great frequency after influenza. In all of these is it probable that the specific cause of influenza also acts, or is it solely the secondary infections which have crept in?

There is probably no other specific infectious disease in which relapses and reinfections are more frequent than in influenza. These are so frequent that they may be almost said to be characteristic of the disease. Not only does one attack fail to confer an immunity, even a very short lived one, but it seems to verily increase susceptibility. A certain degree of immunity against the infection is apparently conferred upon those who are continually exposed to the infection, as in physicians and nurses who are constantly dealing with these cases, but once the initial

attack takes place, even this "immunity by constant vaccination" seems broken through, and for a considerable time thereafter the patient seems to be inordinately susceptible, not only to outside and new infections of the disease, but also to reinfections apparently autogenously induced whenever, for example, the resistance of the convalescent is broken by a depressing factor of any sort. It is these cases in particular which develop the most grave and multitudinous complications of influenza with most frequency and greatest violence.

I have already half confessed my belief that in the infections of this character the original specific etiologic factor of influenza, whatever it may be, plays a part. I have a reason to express for the "faith that is in me."

Whenever the serious complications appear in convalescent cases of influenza it will be usually found that immediately preceding the onset of this complication the patient will have complained of a preliminary nasal catarrh or, as he may express it, of a "cold in his head."

Martland, after a very considerable series of autopsies on influenza cases during the great epidemics of 1918 and 1919 in the American Expeditionary Forces, found that in practically all instances these fatal cases showed the presence in the sinuses of the head, in the frontal, malar and ethmoid spaces, of pus and abundant infected catarrhal exudate. In many instances the amount of this secretion was very large, and yet in a large number of these examples it had produced no recognized clinical symptoms. In several instances otitis media and even mastoiditis had developed in this course without symptoms definite enough to have attracted the clinicians' inqury to the spot.

Martland's observations have been, it is true, but confirmatory of an opinion long advanced by a good many nose and throat specialists, and he has been confirmed in his findings by several other pathologists working on the same type of cases. My own studies of the infection, both in civil and military practice, have fully convinced me that sinus and nasal infection is an essential part of the introduction of the disease, that it persists usually as the longest evidence of the disease, and in my opinion

it remains as the focus of infection and reinfection from which subsequently develops many or most of the complications and sequelæ of the disease. Russell Cecil, in a personal communication, informs me that in his monkeys experimentally infected with influenza, this early and very persistent involvement of the sinuses is constantly present, even though in his experiments the infection was introduced not by supposedly normal avenues, that is, through the upper air passages, but through intratracheal inoculations. These sinus infections, therefore, I would no longer class as wholly due to mixed infections occurring as a chance in postinfluenzal cases, but really as a part of the infection of influenza, and the reinfections lit up usually from these often submerged and hidden sources, are caused in part by the specific infection and in part perhaps even the greater part, by secondarily infecting organisms always found in abundance in the very areas which we have been discussing, especially when catarrhal conditions are present in them. Recurrent and relapsing attacks of the general symptoms and signs of influenzal infection I believe to be caused in precisely the same way—from a reinfection due to auto-inoculation from these persisting foci.

I should not have devoted this considerable space and time to these introductory remarks had I not felt that this conception of the development of the complications and sequelæ of influenza was of elemental importance in the prophylactic and routine treatment of this disease.

The sinus infections are of most primary importance not only because of themselves, but chiefly because of their danger to other portions of the body, and especially because of their direct relation to middle ear, of the mastoid to persistent nasal catarrh, and probably to meningitis also. For these reasons I believe that in every persistent case of influenza certainly, and probably in all others as well, especial therapeutic attention should be directed to the sinuses and every precaution should be taken to prevent the retention in them of infected material.

Perhaps from the foregoing it may seem that I would infer that all cases of reinfection in influenza originated from sinus infection. There is no doubt whatever in my mind but that this

takes place also from the persistent bronchitis and broncho-pneumonia of influenzal origin, but in very many instances the bronchial infections are apparently maintained by constant re-infections from the upper air passages.

More or less bronchitis is an almost invariable part of every case of influenza. Even such cases as make but few complaints of cough or respiratory distress on close examination show, almost without exception, at least some bronchitis.

A review of the autopsy records from the large list of cases mentioned showed that bronchial and peribronchial lesions were invariably present in greater or less degree. We must state, however, that in this particular influenzal epidemic the disease followed almost always the respiratory type with but comparatively few instances of gastro-intestinal or meningeal forms.

A persistence of the bronchitis long after the temperature course has returned to the normal, and the case advanced to convalescence, is the rule rather than the exception, and one of the most annoying, dangerous, and persistent aftermaths of influenza is the subacute or chronic bronchitis which follows it. One of the most insistent dangers of the period of convalescence lies in this fact, for secondary pneumonia, empyema, chronic pulmonitis, lung abscess and bronchiectasis, most common of all, a persistent bronchitis follows this disease. From observations which I was able to carry out while in the military service I am convinced that some of the cases of recurrent or postinfluenzal pneumonia really develop in the course of the chronic bronchitis of influenza from a secondary infection with pneumonia-producing bacteria from other cases. I believe most thoroughly in the efficiency of correct quarantining of these convalescents, in screening of the cases, and in the necessity of masking attendants, nurses, and physicians who pass from case to case among them. The efficiency of this method as compared to the dangers of its neglect have been amply illustrated to me in a comparison of my cival wards with those under my charge while in the military service. I wish to earnestly emphasize the dangers of pneumonic infection to which I believe postinfluenzal cases are particularly exposed when allowed to come into contact while in this sensitized

condition with the discharges from respiratory cases of other types.

Cases of influenzal or postinfluenzal bronchitis, and especially those which have suffered also from influenzal bronchopneumonia should not be discharged from medical supervision, even though long afebrile, until the physical signs of bronchitis have disappeared from their lungs. This may require, it is true, months, and it usually is weeks rather than days before the acute case has subsided.

Where actual peribronchial infiltrations have existed it is naturally in those areas in particular in which the bronchitis persists most obstinately, but otherwise it appears to be chiefly at the bases posteriorly and relatively close to the spinal border that I have found resistant areas most frequently, though they may remain in any part of the lung tissue, or apparently migrate from place to place. I am convinced from the examination of many of these cases with the fluoroscope, or by means of the *x*-ray plate, in addition to the usual physical examination, that in very many instances minute areas of bronchopneumonia may appear and disappear, even without the resumption of temperature or great prostration. The chiefest danger in these cases appears to be that, when for any reason the resistance of the body is reduced, as from climatic variations, from physical exhaustion, emotional crises, etc., an exacerbation of the bronchitis is likely to be set up in the course of which a bronchopneumonia or a bronchiectatic process may be set up.

Lung abscess appears to develop in many of these cases and with a much greater frequency than I had previously thought to be the case. Of course the condition should be fully expected when one recalls that all the essentials for the evolution of this process exist, the infected focus in the chronically infected bronchus or bronchiole, the thick and tenacious mucus tending to plug the tube and check normal drainage, and the surrounding inflamed and devitalized pulmonary tissue.

In my recent influenzal experience the formation of bronchiectatic cavities or lung abscesses has occurred most frequently in the bases of the lungs, and nearer the spinal rather than the

peripheral borders. I refer here, of course, exclusively to the pulmonary abscesses and not to those which originate in pleural inclusions which finally penetrate into the substance of the lung.

In practically all the persistent cases of postinfluenzal bronchitis an apparent pulmonary infiltration may be made out from time to time either by physical signs or by fluoroscopic or x-ray examinations. In most cases it will be found that there is a thickening of the tissue in the central portion of the lungs, perhaps more extensive on one side than the other. There is frequently much evidence of a chronic congestion of the lung, again both evident on x-ray and on physical examination, courses of temperature commonly are present, and in some respects the case may quite suspiciously resemble the onset of a chronic ulcerative pulmonary tuberculosis. I have seen numberless cases of this kind in which it is quite impossible to differentiate except from the final clinical course. Proper measures of treatment fortunately differ little in either case. It is the knowledge of most medical officers connected with the internal services in the army hospitals that tremendous numbers of these cases which have, on the basis of x-ray and clinical signs, been temporarily diagnosticated as pulmonary tuberculosis, who have, under appropriate treatment or even on none at all, entirely cleared and with a rapidity entirely inconsistent with cure in pulmonary tuberculosis of so wide-spread a type. I wish to particularly warn men who have not seen many of these cases against making hasty diagnoses of tuberculosis in the postinfluenzal cases until unmistakable signs have appeared, and even to wait in most instances until it is possible to demonstrate the tubercle bacillus.

Suitable climatic conditions are quite as valuable in these cases and produce quite as startling results as may ever be the case in tuberculosis. I know of no one measure which will produce in most instances the immediate relief of cough, cyanosis, dyspnea, and general malaise associated with the cases, like a change to a suitable climate. Postinfluenzal cases, however, do not, as a rule, do well in cold climates, even no matter how apparently desirable in other respects. Warmth, preferably associated with more or less altitude, is by far the more desirable,

though very many cases do extremely well in such climates as Florida, southern California, or even at Atlantic City and Lakewood. The marvelous improvement which occurred in the cases of this nature which were sent from the North of France down to the leave areas in the South, Cannes, Nice, etc., was very striking indeed.

Many of these cases demand digitalis before they entirely clear up, even where there is no apparent disease of the heart, but only a certain degree of chronic pulmonary congestion. Where the sputum is tenacious and thick, ammonium gives unquestioned relief, and in the latter stages the iodids also improve matters very much, but the condition is essentially one which demands climatic change from the humid and chilly areas in which this complication is most likely to develop, and in which rest and generous feeding are factors of but little less importance. I think that it is very well, however, to impress particularly upon those who have not had a wide experience with these cases the great importance of checking the violence of the cough which is presented in many patients. There is no doubt in my mind but that when cough is allowed to proceed unchecked, it increases the congestion of the lung, favors the increase of emphysema and the spread of bronchitis, and peribronchial infiltrations, with all that this entails.

Where cases as the above are allowed to proceed without proper attention, and particularly in those instances where the disease has been associated with bronchopneumonic infiltrations, or where the lung has been compressed more or less as a result of a pleural exudate, or perhaps rendered more or less atelectatic through a venous thrombisis, or through the plugging of a bronchus by a tenacious plug of exudate, fibrotic alterations are very likely to develop and permanent changes are wrought in the lung parenchyma of the most serious possible nature. Many instances of this character have fallen under the observation of the speaker during the past three years, and I wish to particularly emphasize the importance and frequency of the condition. If it is to be prevented it must be by prompt action before the fibrosis has proceeded far, and particularly before it has become

complicated with a diffuse bronchiectasis which is almost invariably finally associated with it. Where facilities exist it is always advisable to resort to the fluoroscope or x-ray as well as frequent physical examinations in cases of persistent postinfluenzal bronchitis in order that minor degrees of compression and atelectasis may be early detected and proper treatment installed so that the serious condition of pulmonary fibrosis and bronchiectasis may be avoided whenever possible.

Pleural exudates of all forms are very frequent in most epidemics, almost universal in some. It is still a mooted question in the minds of most clinicians when a simple pleural exudate should be evacuated when it is of insufficient size to seriously embarrass respiration, and when by diagnostic tap its nature is known to be such as not to imperil in case of its retention. In my opinion whenever compression of the lung, and this is particularly likely to occur in encysted exudates, is sufficient to cause undue dyspnea on slight exertion, and so to invite congestion, atelectasis and organization, the fluid should be promptly removed and breathing exercises or other suitable pulmonary gymnastics introduced which tend to expand the lung tissues and therefore prevent pulmonary fibrosis.

Pulmonary fibrosis and atelectasis is also invited quite certainly in those instances when the surface of the lung is covered by a very thick exudate undergoing organization, in the process of which contraction of the lung and the formation of extensive bands of fibrous tissue is invited. This is another argument for the relatively eaıly removal of exudates from the pleural cavity when contraindicating circumstances do not exist.

The whole question of the management of pleural exudates is perhaps a bit wide of the subject of this talk, but it is such an important and so inviting a topic that I cannot restrain myself from saying something concerning it here, particularly as it has occurred with considerable frequency after certain of the recent influenzal epidemics, though not in my experience in the type of the past year.

My experience has been such that I believe that all exudates should be promptly evacuated when respiratory distress is caused

by their presence. I favor frequent and repeated aspirations to open drainage, except in those instances when the pus has become thick and tenacious, and particularly in those instances when the pneumococcus is found in it. When the organisms demonstrated by diagnostic tap are of the streptococcal group, I much prefer to delay operation and to thoroughly try out repeated aspirations. I have been forced to these conclusions as a result of the study of the mortality lists under the two procedures, particularly in my own cases.

In these talks I am keeping away from the discussion of influenzal pneumonia just as much as it is humanly possible for an enthusiastic clinician to do, for the reason that so large a subject cannot be adequately presented in so general a series of lectures as these, and also because the importance of influenzal pneumonia is so great and its occurrence so frequent that we have all almost come to look upon it as a part of influenza and not merely as it only is, a complication of the infection.

But the clinician must be especially continually on the outlook for small areas of bronchopneumonia. They may very easily escape the notice of even very keen diagnosticians unless assisted by the use of the fluoroscope, and it is quite safe in my experience to assume, as the clinician has in many cases come to do, that where an unexplained run of temperature persists and signs of bronchitis are present, if the temperature course persists over three days without a drop below or to the normal at some time during the day, other inflammatory foci wanting, that we are certainly justified in assuming that we are dealing with a bronchopneumonic process, in addition to whatever bronchitis may be demonstrable.

We must also never forget the relative frequency with which more or less pulmonary fibrosis occurs in the postinfluenzal lung, especially if it has been the seat of a bronchopneumonia, a severe bronchitis, or if it has been rendered more or less airless for a considerable period either from pleural exudate, or some other manner of compression, or as a result of a pulmonary thrombosis which is by no means an infrequent sequel of influenza.

More or less bronchiectasis is the natural expectation when

pulmonary fibrosis or long-standing bronchitis has been present; perhaps a likelihood toward it is present as a result of the cough which sometimes persists after influenza, and which may even be of so remote actual origin as from a persistent laryngitis. Wherever bronchiectasis is, or may be, pulmonary abscess is to be expected. It is probably much more frequent than we had often thought to be the case before we had such frequent recourse to the fluoroscope and *x*-ray, and its occurrence after prolonged influenzal infections, as has been shown in the epidemics of the two past years, is particularly frequent. Doubtless many of the abscesses take care of themselves. I am sorry to say that my experiences with those which have been attacked surgically has not been very flattering.

I have just mentioned in passing the frequency of persistent laryngitis in influenza. Influenzal laryngitis, tubercular laryngitis, and new growths of the larynx can be differentiated only by actual laryngoscopy, and sometimes even then not so easily even in the hands of experts. Be cautious in your prognosis, therefore, until you have indisputable data on which to base it.

Before we leave the respiratory tract let us again mention the frequency with which pleural thickening and pleural exudates occur after influenza, and especially in certain epidemics of it, It is not the treatment of these conditions now which gives us the most difficulty; it is the detection and recognition of them.

After the respiratory complications of influenza and the direct extensions of sinus infection are considered, doubtless the most frequent and serious complications of influenza are those of the heart.

I am quite certain that before the two last great epidemics of influenza the impression was very prevalent among internists that tuberculosis and particularly chronic ulcerative pulmonary tuberculosis was among the most frequent convalescent complications of an influenza. I am equally certain that since this last great epidemic this opinion has been very much modified, particularly by such of us who were able to follow our cases either in person, or statistically in the Army records. As already said, a persistent type of chronic pulmonitis, bronchopneumonia, or

bronchitis occurred with tremendous frequency after the influenzal bronchopneumonias in particular. In very many respects, particularly in its physical signs and in its *x*-ray findings, this did very closely simulate what we had expected, namely, tuberculosis of the lungs. The clinical course of the cases, however, and the failure of the tubercle bacillus to appear in the sputum soon set these cases aside, so that in so far as we may judge from the epidemics of the past two years, tuberculosis of the lungs has not been a frequent sequel of influenza. It is, of course, quite possible that this may have been but one of those peculiarities of this particular epidemic, for no other great infection shows more definite tendencies to assume definite and characteristic yearly types than does influenza, but the fact remains that tuberculosis has not been a frequent complication in adults or elderly persons in the form of the disease with which we have been dealing in the past two years. Maurice Fishberg calls it even a rarity.

In regard to children, with whom my experience is very much more limited, I cannot say, nor would I have it assumed that I do not very frequently find that old tubercular subjects, even clinically healed cases, do not frequently present a flare up after their influenza, but my point is simply that notwithstanding the great damage committed on the respiratory tissues by the influenza, it does not apparently materially sensitize to the active outbreak of an acute pulmonary tuberculosis. It goes entirely without saying that, of course, those weakened down by the influenza, if already infected with tuberculosis, frequently became active subjects after the influenzal attack.

It has been stated by some, notably by Hart, that the number of cases which showed cardiac deficiencies after the great epidemic of influenza in America in 1918–19 was very small. It is impossible for me to dispute this statement, particularly coming from so well accredited an authority, because I was absent from America during that period, but it has been my fortune to see a very large number of cases of cardiac deficiencies, which are alleged to have followed attacks of influenza during this epidemic. particularly in my consulting work, especially in physicians and

physicians' families. It has seemed to me that very probably the reason that Hart reports so small a percentage of cases may have been because he secured most of his material from hospital patients who had perhaps failed to report later on with their cardiac defect, since in my experience the cardiac defect has very commonly not become obvious until some time after the clinical conclusion of the case, at which time most acute cases are discharged from the hospital. I have further been persuaded to this conclusion by the fact that in the military service, where necessarily a much more prolonged supervison of the patients is possible, it was found that the postinfluenzal heart often did not appear until a considerable time after all supposedly active evidences of the disease had subsided. Since this coincides precisely with my experience in dealing with private and consulatation cases, I assume that this explanation is probably the correct one.

W. W. Hamburger, at the last meeting of the Association of American Physicians, reported a most interesting and well-worked-up series of postinfluenzal cardiac conditions, which fully bear out my conclusions in regard to heart involvement in influenza.

As to the form of cardiac defect which appears most commonly in postinfluenzal conditions, endocarditis has been very frequent in my observation except in those instances in which a streptococcus infection has developed as a complication, or coincidentally taken place. Where the Streptococcus hæmolyticus or the Streptococcus viridans was found in the circulating blood, endocardial infections were, on the contrary, quite frequent and expectedly so.

The usual story given by these cases has been that of a slow convalescence from the active influenzal infection, in the course of which precordial oppression or cardiac irregularity develop. Percussion of the cardiac outlines frequently may suggest a certain degree of cardiac enlargement, but in no case in my experience has this finding been verified by the fluoroscope. Arhythmia, if present, usually develops as a result of some exercise or of some emotional strain, often but a very slight one, though it may persist through resting periods also. The type of

arhythmia cannot be defined, since it has been very variable; in some instances it has apparently been the manifestation of an increased muscle irritability with contractile impulses apparently originating elsewhere than in the normal node; in other cases it has seemed to be precisely a paroxysmal tachycardia, and in still other cases to be a very slow action in which both auricles and ventricles partook of the slowing, definitely not a condition of heart-block. I have seen very few of these cases at autopsy and hence I cannot speak authoritatively as to the lesion probably present, but insofar as one may judge from analogy and from clinically similar conditions with which I am more familiar, the condition is one of a myocarditis associated in most instances by a myocardial degeneration. As before stated, most of these cardiac defects do not appear immediately during the period of fever or prostration, but at a time considerably thereafter.

Assuming this to be the anatomic condition present, it is quite as would be expected that slight exercise or emotion develops a dyspnea altogether out of proportion to the exciting factor. This is accompanied by pain in the region of the heart, or often reflected along the same zones or lines seen in anginal or dilating cases. Where the condition is very marked or persistent, a certain amount of cyanosis is likely to appear, particularly in the hands, feet, and face. Edema of the feet and ankles is not uncommon.

Auscultation of the heart is very often confusing. Not only do the signs revealed by auscultation vary much from time to time, but they are of so indefinite a character as to cause great dispute as to their mechanical origin among even the most skilled diagnosticians. Not once alone but frequently I have found true endocarditis diagnosticated, particularly lesions of the mitral valves, while others examining at the same time have asserted that the murmurs present were myocardial in origin or even hemic.

Suffice it to say that I have never found the murmurs present under these conditions, hemic infections having been excluded, nor have I known them to persist after the clinical signs of the cardiac defect have gone. I believe that these murmurs are

usually muscular in origin, and that most of them arise from inco-ordinated contractures of the cardiac muscle. While many of them are doubtless due to true myocarditis, for the greater part I believe them to be degenerative, and if gross dilatation does not take place, I believe that in most instances at least the lesions are curable and permanently so.

A point upon which I lay great stress is the character of the first or muscle sound of the heart in these cases. It will be found to vary tremendously in its character and force; at the same time it will be found that the systolic blood-pressure varies considerably from moment to moment, particularly when during the recording the patient is submitted to various physical, emotional, and depressing stimuli. To my mind the close study of the muscle sound of the heart is one of the most satisfactory methods of determining a myocarditis or myocardial degenerations.

The treatment of this condition is of the utmost importance not only for the immediate relief of the patient's discomfort and fear, but particularly because of his future service. I do not think that there can be a more serious condition leading on to dilatation of the heart and chronic muscle incompetence than this if it be allowed to progress. In my opinion the correct treatment must be based on the primary assumptoin that the lesion present is in all probability either a myocarditis or a myocardial degeneration. Dilatation of the heart must not be allowed to take place. No unnecessary physical or emotional strain should be permitted to be laid on the heart. If need be, the patient must be confined to bed at least until such time as he is able to sit up, walk, and talk without the appearance of arhythmia, dyspnea, or cyanosis. Rest is the cardinal feature of the treatment. Digitalis, strophanthus, and other similar drugs I have found to be of little or no use. In the first place, I have not been able to improve the symptoms or signs of the heart disturbance by their exhibition, and in the next, from our knowledge of their action, I fail to see how theoretically we may benefit the condition through this avenue.

The bromids, morphin, codein, and the like may, of course, be symptomatically and appropriately employed in these in-

stances, but purely for their symptomatic effects. It is possible that in the late stages the iodids may be well employed, especially when a tendency to fibrous deposit may be justly thought likely to occur in the heart muscle, but in my experience just two important agents are to be successfully employed as a routine—rest and nourishment. This last I believe to be of very great importance, but since it forms so essential a part of the treatment of nearly all the complications of convalescent influenza, it need not be specified at this point. The great thing is to protect the heart in just so far as possible from every unnecessary strain until such time as it is sufficiently self-recovered to sustain its efforts and to meet its responsibilities in a normal way, without damage to its own structure. Cases carried along under these lines will yield most surprising results, and the most skeptical will be not infrequently surprised to find how very commonly lesions, which from their physical signs seem definitely to be endocardial, completely disappear.

Just as prostration is one of the cardinal and most characteristic symptoms of the active phase of influenza, so mental depression is one of the hall marks of the period of convalescence. There are very few cases which fail to show this at least to some degree, but the severity of the mental and nervous depression is often no measure of that of the causative infection. On the contrary, in some instances very pronounced grades of depression follow cases of very mild severity, and of short duration, and, on the other hand, only lesser grades may occur after apparently very toxic forms of the infection.

Naturally enough the mental depression is likely to be most marked in those persons naturally given to melancholy and to forebodings and worries, but, on the other hand, it not at all infrequently occurs in very marked grade in persons naturally of a buoyant and optimistic temperament. Its constancy of occurrence is altogether too great to permit the idea that it is a chance complication or sequela, but shows quite definitely that it is an essential part of the disease; while most marked in those of an easily unbalanced nervous temperament, very severe grades of melancholia and depression may be seen in persons who have

never before indicated anything in the nature of mental alienation. Actual mental aberrations, delusions, hallucinations, and particularly insomnia, and sleep disturbed by all manner of worries and oppressions are seen. Suicidal impulses in persons previously perfectly normal are quite frequent; most extravagant distortions of logic, "grouchiness," petulance and irritability, improper judgment and utter disregard of proportions in mental ways are characteristic in various cases. Writers find themselves recording ideas or situations which will not stand for a moment the test of their wholly well moments; scientists attempting problems find their reasoning wrong in abnormal channels, and their technic faulty. The work value is tremendously reduced.

Most characteristic of all, indeed, is the inability to do work, to concentrate, or to apply the mind along even familiar channels of thought and effort. Even slight mental effort causes a very disproportionate degree of exhaustion, and the length of time during which one may work is much reduced.

The exhaustion is not only mental, but is directly combined with a proportionate or even greater degree of physical exhaustion. In this respect it differs very materially from the conditions which are commonly seen in actual mental disease. Not only does the student find himself mentally exhausted after a short period of study, but a very marked grade of physical exhaustion accompanies. This association of physical with nervous exhaustion is perhaps most strikingly shown in such occupations as artists. The musical performer not only finds his spirit exhausted and erratic, but his technic falls proportionately off also, so that he is physically as well as mentally incapaciated for full efficiency.

A few, but only a few, cases show active phases of mental disturbance, ungovernable temper, hysteric outbursts, aggressive irritability and quarrelsomeness; the general tendency is definitely toward depression and inaction.

I think that most of you who have seen many instances of encephilitis lethargica are prepared to agree that the cases appear most frequently and most severely, that is, in the epidemic type, after epidemics of influenza. There are those who are convinced that encephalitis lethargica is but a manifestation of influenza,

and that it represents one type of the so-called meningeal form of the disease. It has been my good fortune to have seen a large number of cases of encephalitis lethargica during the past two years, and I utterly fail to see a further association between this disease and influenza, except that the one follows the other with great apparent frequency. There are, however, certain forms and cases of depression which occur after influenza which very strongly resemble, in so far as symptoms are concerned, certain types of encephalitis lethargica. Many cases of postinfluenzal infection are depressed not only mentally to the point of indifference and negligence, but the spinal reflexes are also reduced in activity to such a degree that the symptomatic stimulation may be very close. I have never, however, seen a case of postinfluenzal infection which has shown a paralysis, such as is typical even though transitory in encephalitis. I have never seen the depth of mental clouding which is usual in encephalitis, nor have I seen the definitely lost and abnormal reflexes which typify many instances of encephalitis in cases of influenza. As is well known in encephalitis lethargica, very definite and easily demonstrable pathologic lesions are present, whereas in the postinfluenzal depression the lesions, if at all detectable, are not more than cytoplasmic alterations in the ganglion cells.

Although there is still lacking the definite pathologic proof, the assumption is that the depression of the postinfluenzal stage is due to cytoplasmic alterations in the ganglion cells, perhaps also in their dendritic synapses, which are the direct result of the toxemia of the infection. In so far as we know from negative cerebrospinal fluid findings and counts, and from the histolologic examination of tissues postmortem, inflammatory changes are absent or, if present, accounted for by some secondary condition.

The duration of this condition of exhaustion or depression is extremely variable. This appears to depend somewhat on the individual severity with which the infection has poisoned the individual, but, as a rule, youth stands it far better than the adult or senile, and these last two recover much more slowly from the condition.

In many of these cases one is strongly impressed with the

possibility that many of these nervous, mental, and indeed physical exhaustive symptoms also may be due to actual involvement of the ductless glands. Cowie and his associates at Ann Arbor believe that they have demonstrated definite endocrine defects in cases of influenza and influenzal pneumonia; they are probably entirely correct, and perhaps many of the symptoms which we are now discussing may be the result of such direct lesions.

As to the prevention of this disagreeable train of symptoms in influenza, little appears to have been accomplished. If the patient is kept in bed, nourished satisfactorily but not too much, with his excretions well up during the activity of the disease, the condition can none the less apparently not be averted, nor can it be definitely mitigated, except by time and diversion, in so far as my observations go, once it has developed. Much remains then to be accomplished in the treatment and prevention of this important sequel of influenza.

Rest appears to be the most important factor in the treatment of the postinfluenzal exhaustion. This includes both physical and psychic rest, the one appearing to be no more indispensable than the other. The patient must be encouraged to take all the rest and sleep that it is possible for him to obtain. Where through irritations, worries, or due to a persistent cough, or other factors this cannot be obtained, naturally the use of drugs, preferably, of course, of the bromid or cannabis indica class, is to be advocated, notwithstanding the fact that in many cases all sedatives, in my opinion, delay the recovery from the mental depression. There is no question in my mind as to the desirability of alcoholics in properly selected patients during these manifestations. Quiet, a well-aired and attractive sleeping apartment, the seashore, or the deck of a boat may be utilized to excellent effect. Easy and pleasurable travel by boat, canoe, in automobile, or by pack train, all according to the desires or customs of the patient, may bring about a most satisfactory result and, at the same time, contribute that other very desirable element in the cure of these cases—diversion and recreation. Pleasing travel, never too hard from the point of physical severity, is one

of the most happy and sensible ways of treating this condition in almost all of its forms, and while the type and direction of the travel must of course be fitted to the desires and possibilities of the patient to a very large extent, in many instances something utterly new, strange, and absorbing may greatly assist in taking the patient's mind from himself and his woes, and go far in itself to accomplishing a cure. Change of surroundings from the hospital to home, or a well-ordered sanitarium, to a seaside or mountain resort, a change of nurses and of personal attendants, is also most beneficial in aggravated and persistent cases.

As a rule, I have found that an abundant diet, one combining a high grade of food value with tastiness, and frequent gastronomic surprises, is best adapted to these cases. Forced feeding is permissible in but few instances, but a very liberal diet is both desirable and possible in nearly every instance.

I am not particularly enthusiastic as to the drug treatment of these cases, though drugs should be symptomatically employed as indicated—stomachics, carminatives, and the like. Alcoholics I believe, too, possess real value, especially for those who have been in the past accustomed to them. Wines and beers are, of course, the preferable forms to use.

Where respiratory or circulatory conditions do not contraindicate, the discrete use of tobacco for those accustomed to it may serve a very good end. Nothing perhaps contributes more to the comfort and solace of an appreciative smoker than a temperate return to his tobacco.

Coffee and tea, I believe, are advisedly employed except where there is a tendency to wakefulness, and an undue sensitiveness to these stimulants in preventing sleep. I much prefer to use the tea and coffee as adjuvants to the dietary than as mere prescriptions of caffein, theobromin, etc., in their drug form.

The mental management of these cases is very important, and the astute physician is never unmindful of it. The use of visitors, of properly selected books, of music and art, all are contributory factors of very definite and real value, but a further discussion will lead us here too far afield from the more definitely medical side of our problem. The object of the treatment must

be held firmly in mind, to give the brain and ganglion cells rest, nourishment and diversion, to excite pleasurable and pacific in contradistinction to depressing and aggravating factors, but even with all the most favorable circumstances possible, the convalescence from these complications may be exceedingly long. Prognosis as to time is always most uncertain.

Notwithstanding the fact that the physical depression after influenza is often very severe and almost always present, it requires no particular discussion from me at this time for the reason that it is in no respect unlike that which follows practically all of the long-standing infections, or the severe acute ones. It is true that it is often present to a degree which appears altogether out of proportion to the severity of the initial infection, but this is also true to a considerable extent of other postinfectious conditions as well.

In very many cases the grade is sufficiently severe so that it is impossible for the patient to return soon to his occupation, particularly if it be one in which a considerable expenditure of physical effort is demanded. Accuracy and close co-ordination of physical effort appear to be chiefly diminished.

The treatment is simply that which is applied in all instances of postinfectious disability, except that perhaps it may be required for a longer period of time and the condition may be found more resistant.

Briefly, the most satisfactory treatment consists of adequate rest and sleep, abundant and simple nourishment, and of a gradual return to the complete exhibition of physical effort customary under normal conditions.

There can be no doubt but that the most insistent complaint on the part of the average patient convalescent from influenza is that of muscle pains and of muscle stiffness. The location may vary in different persons and in the same patient at different times. In some cases the pains may be almost solely limited to a single group of muscles, as to the lumbar group, or the cervical muscles, giving the typical picture of a torticollis or of a lumbago, but more often they are not so definitely localized, but occur in different parts of the body, moving from time to time.

As to the etiology, the chemistry, or the morphology of this phenomenon, we know nothing. It is true that in certain instances, as in some of myalgia, small round-cell infiltrations of the muscle or tendinous areas is found, but in others not, so that we have nothing to offer as to a real and definite pathologic explanation of one of the most constant symptoms and sequelæ of this infection. It is quite true that we may attribute these pains and the resulting stiffness to the same condition which arises during the height of this, or for that matter of almost any other infection, but this explains nothing, since this also is not understood. We may also say that it is due to the presence of a toxin in the blood or lymph, but this is again a purely suppositious condition and not capable as yet of demonstration. But at least we are able to treat these cases with benefit and relief, and an adequate explanation of the pathology or chemistry being wanting, we must content ourselves with a study of the means for its relief, a much more interesting and thrilling topic from the viewpoint of the patient.

The patient is himself soon aware that too frequent or too violent muscle or tendon exercise accentuates these pains, and in many instances this is so very evident that mechanical fixation of a group of muscles or tendons chiefly effected must be arranged. But this should be continued for only the absolutely necessary period of time, for there can be no doubt but that the greatest final relief is afforded by motion of the affected part, not violent and tiring motion, but gentle and persistent. This is often best effected by massage or by passive movements; later on by gentle exercises and by bathing, especially with warm or hot water. During the most active stages of the condition the local application of heat in the form of the electric pad, hot-water bottle, or the like, may give tremendous relief. Cold applications may also effect the same temporary end, but it has been my experience that whereas both heat and cold give alike relief of a momentary nature, in my belief, the more permanent results are alone attained by the heat. Local vesicants, the mustard plaster, applications of menthol, thymol, capsicum, and the like, or even dry or wet cupping, may give the same result, but, as a rule,

the relief afforded is but temporary and not progressive in any degree.

Although again we are unable to explain perhaps, on a pharmacologic basis, the relief afforded by the salicylates, the fact none the less remains that we have in this group of drugs an agent more potent in the relief of these postinfluenzal pains than even the active anodynes, as morphin and codein, and, of course, infinitely safer to employ, if used intelligently, and with far fewer bad after-effects.

It goes without saying that a considerable selective discrimination must be exerted in the choice of the best form of drug, and it is always necessary to bear in mind that in this disease in particular, a diseased heart muscle is very likely to be found, but if the personal idiosyncrasies of the patient be studied, some one among this considerable list of drugs will be found which can be employed in efficient doses without in any apparent way delaying recovery, or causing damage to other organs of the body. My chief favorite, because among the very safest, is sodium salicylate, and if because of gastro-intestinal irritation, it be possible to employ it by stomach administration, it may be given, if necessary, intravenously or even more satisfactorily by rectum.

We must also not forget the utility of colchicum, atophan, and of the alkalies in many of the cases, especially the more chronic ones. It will not uncommonly be found that in instances which fail to respond favorably to the salicylates, many quickly subside under this group of so-called antigout medicaments.

The great frequency with which Zenker's degeneration occurred in the muscles of the abdomen, particularly near the insertion of the recti, in the psoas and sometimes in the abdominal obliques also, in the epidemic of the past two years has been very striking. Never in my experience has anything like this frequency of occurrence been noted before. It seems almost to have been one of the hall marks of the recent epidemic in all parts of the world. This has led, of course, to the finding of abscesses, or areas of hemorrhagic softening in these locations with considerable frequency in convalescent cases of the disease, and so frequently did this occur in one area that the attention of

surgeons had to be called to the lesion, because of the fact that so many cases were surgically diagnosed and treated as though of intra instead of extra-abdominal origin.

Although in my personal experience I have seen these areas of softening only in the lower abdominal region, that is, in the recti, the obliques, or in the psoas muscles, if our theory as to their manner of formation is correct, there is no reason why they might not occur elsewhere, and it is certainly wise for the clinician to be on the lookout for them not only in these but in other locations also.

The question very naturally arises if these areas of muscle degeneration may not bear some definite relationship to the process responsible for the muscle stiffness and pain which we have just discussed; we have no answer for this question. It is but one of many which are suggested to the studious clinician in regard to this most interesting infection.

There can be but very little doubt that the joint pains and neuralgias which so frequently follow influenza are of precisely the same nature as the muscle pains and stiffnesses which have just been discussed. As a rule, they are more or less combined in the same cases. Articular or periarticular infiltration is only rarely demonstrable in these cases, and furthermore almost always the measures which serve to alleviate the one condition relieve also the other. When we come to a full explanation of the etiology of these conditions it is highly probable that we shall find them due to one and the same process.

The neuralgias and probably the true neuritis also which occasionally appears in this infection I believe to be due also to precisely this same condition. It is certain that therapeutically they are relieved by measures along the same line of treatment and by no others.

In so far as actual cure of these complications is concerned, it appears to me that a full diet is one of the most certainly beneficial measures. Removal to a bland and, most desirable of all, to a dry and warm climate accomplishes very much in the relief from these conditions. Rest and relaxation are real therapeutic measures, and we can look upon the drug treatment

as only adjuvant, but very often most necessary and imperative because of the tremendous symptomatic relief which properly selected drugs give in these cases. It is very probable that others have found, as I have, that often best effects are reached in the use of the antineuralgics, antigout, and antipain drugs in general if the form of the drug be frequently changed, for all of them tend to induce a tissue or chemical tolerance which sooner or later causes them to lose their relief-giving properties.

As is well known all of these conditions tend to become chronic if not rather promptly relieved at their outset. Though not nearly so frequently as in rheumatic fever, in gout, and the like, atrophies of muscle take place, especially in neglected cases, and chronic infiltrations take place about joints and tendinous insertions. It is of, course, possible, or even probable, that these instances are such as are combined with a tendency toward arthritic or some other disordered type of metabolism, which renders certain cases especially susceptible to this tendency. Be this as it may, it does occur that certain cases of polyarthritis chronica date their onset from attacks of influenza. In several instances of this apparent character we have employed with an encouraging degree of success the intravenous injection of foreign protein, using after the manner advocated by Joseph Miller of Chicago the typhoid vaccine for the purpose. Although I do not allow myself to become unduly enthusiastic over the method, I confess freely that in instances where, from the antra, internal ear, or elsewhere, an exudate developing in the course of the influenza has continued, in these instances of myositis, neuritis, arthritis, and the like, I believe that the preparation and administration of an autogenous vaccine is definitely indicated, and that the method offers a justifiable amount of success, and I am willing even to go further and to admit my advocacy for the use of vaccines in prolonged cases of influenza, whenever persistent exudates are present. I would not have you infer from this that I believe that the exudate is necessarily specifically influenzal, but only that such treatment does definitely assist in the clearing up of many of the conditions which follow in the trail of influenza and its multitudinous complications.

Our great problem is, of course, How may we prevent or minimize these sequelæ of influenza? Are there any means which we may take whereby we may prevent reinfections or exacerbations of the disease after the initial attack? I believe that we may definitely answer this in the affirmative. Few experienced clinicians will dispute the advisability of rest in these cases. Early confinement to bed is one of the most important steps in the limitation of the disease beyond question. Should the temperature of the sick room be cold, as is most desirable in pneumonia, or warm? Moist or dry? In my opinion these are quite important matters. In my experience it is better in this disease, even when complicated with a pneumonia, to have the temperature of the room at about 70 or 72 degrees, and if possible the air should be dry in preference to moist. These are points of much import, also, when the question of climate in convalescence comes up for determination. I believe that from the very outset it is very important to treat the nasopharyngitis, and close attention should be paid from the very first, and particularly during the stage of convalescence, to the proper drainage of infected sinuses. I am much inclined to feel as yet that this is usually safer in the hands of a well-trained specialist than in those of the internist, who is usually altogether too skeptical in regard to these methods, but operative measures must be resisted unless imperative.

The management of the cardiac complications when they occur presents, for example, considerable difficulty. It is impossible under these circumstances to advise outdoor recreation, riding or walking, nor in many such instances is it even advisable to undertake any very extensive changes in climate. As a rule, rest is the most important measure to provide for the heart, rest both physically and emotionally. Iron, perhaps mild doses of the iodids, may be beneficial, but digitalis, caffein, atropin, and the like are contraindicated in so far as the heart itself is concerned, except as they may be required for emergency purposes. Exercise must at first be very much limited and closely observed. It may be necessary to start it in with passive movements, massage, Nauheim baths, and the like, later adding voluntary effort,

walking on the level, and so progressively on. When the heart muscle has been seriously compromised, months may be required for a restitution to its maximum efficiency, and in many cases the heart remains permanently disabled. Very much depends just here then on medical care, and the advice which the patient follows out.

Questions of operative procedures on the internal ear, the mastoid, the drainage of the sinuses, etc., must be put up to the specialists, but the internist on the case must always hold well in his mind the lowered general resistance of his patient and the increased suffering, depression, and absorbing surfaces in unnecessary operative procedures. I am strongly against anything in the nature of reparative work being done on the nose or throat at this period of the infection, or for that matter even for a considerable period after it, or in the presence of epidemics even on uninfected patients. The speaker has seen several instances in which it is believed that a serious local and general septic condition was induced by such meddlesome operations. I do not, however, wish in the least to interfere in such emergency operations or drainage procedures as may seem necessary.

We have found of all the conditions likely to arise in the convalescence of influenza, that the most difficult phases to manage are the mental and physical exhaustion, and particularly those instances where both are combined in the same case. If, coupled with this condition, is a fairly complete knowledge of the possibilities in the way of complications, as known by physician and nurse, the patient's treatment becomes a most difficult matter. Environment is most important. If possible, the patient must be put under congenial and not irritating surroundings. People who irritate or annoy him must, if possible, be excluded from the sick room. The physician in such instances has a social problem of equal importance to the medical in very many instances. The patient's life must be so ordered that he is not allowed to be aware of his physical or mental exhaustion. If possible, his day must be so arranged for him that he is happily occupied most of the time. Yet, it will be found in most instances that he is not equal to much in the way of emotional or

mental effect. Sleep and rest must be encouraged, if necessary, by the milder sedatives.

One hesitates nowadays when the recommendation of use of the various ductless gland products is suggested. I suppose that we all use them either openly and experimentally or surreptitiously and doubtfully, but there is much in this degree and type of depression to suggest, as Cowie states, endocrine defect, and I believe that important discoveries await us along these lines, and the administration of thyroid, pituitary, and at times of adrenal extract have seemed at times to have helped my patients, but it may have been coincident and not causative.

Most cases have a very poor appetite. This is unfortunate for the reason that the feeding of these cases is a very important matter. It is striking in this disease how relatively immune the gastro-intestinal tract is, except in those peculiar cases of the so-called gastro-intestinal type of influenza, and except in these instances no reason exists contraindicating a liberal diet. The proteins, sugars, and fresh green vegetables are usually preferable, but ingenuity must be exercised in order that the patient's appetite does not cloy from monotony or because of a distasteful manner of serving food. The fresh fruits are very acceptable in most cases.

May I summarize what I have tried to say to you during these hours in the following sentence. I believe that many of the complications and sequelæ of influenza really represent re-infections in which the specific virus of the disease is concerned, together with many mixed organisms. I believe that, in very many instances, these reinfections are autogenous, and that they occur from retained infected secretion in the sinuses of the head, and in the respiratory channels. I believe that careful treatment which takes cognizance of this possibility is met by a lessening of complications, and of convalescence time, and by a lessened degree of exhaustion. I believe that in the treatment of the sequelæ of the infection old infected foci must be cleaned out, and that otherwise, except for such special medication as special signs or symptoms may demand, that change in climate, generous diet, and mental and physical rest are our most efficient measures of cure as well as of prevention.

CLINIC OF DR. S. W. BANDLER

Post-Graduate Hospital

PUBERTY AND CLIMACTERIUM. A STUDY IN ENDOCRINES

Up to and before the period of pubescence the glandular or follicular portions of the ovary have not been active as far as menstruation is concerned—at least not as a rule. The interstitial and glandular ovaries have, however, been performing some of the functions which are related to the development of the secondary sex characteristics, the most noticeable of which characteristics are the future mammary glands. If we at this time compare the frame, outline, and typical locations of fat distribution of the boy and girl we see differences sufficiently marked to realize that they, as well as the differences in tastes and emotions, are due to the fact that the ovaries in the girl and the gonads of the boy must be—as they are—among the responsible factors and that these differences have occurred through the medium of the ovaries on the one hand and the testes on the other. Up to this time, too, pineal gland, the hypophysis, the parathyroids, the thymus, the thyroid, the adrenals, etc., have been contributing their internal secretions, making and molding the child's body, visceral, and sex structures, and—what is not least in importance—the mind or psyche.

The anterior pituitary is especially related to the growth of the frame, of muscle, and the development of the brain; the posterior pituitary is particularly related to the development of the sex organs, muscular structures, and to metabolic processes, etc.; the thyroid is the great activator; and the normal action of the thyroid is of the greatest importance in promoting those trophic and nutritional changes in the brain which lead to the

development of a good mind, good memory, etc. An underactivity of the thyroid is responsible not only for retarded physical growth and for the various degrees of myxedema and cretinism in children so often seen, but, in the absence of all physical manifestations of a marked character, it is responsible for mental sluggishness, for inertia, for lack of energy. Such children tire easily over physical or mental work, are sleepy or slow in their movements, they yawn over their school work, they get up late and dress slowly, and are quite different from the normal, healthy, active child, anxious to go about its work. These children are scolded and called lazy, stupid, "fathead," when all they need is the recognition of the condition and the administration of thyroid extract or pituitary anterior or suprarenal extract in small doses.

The hyperthyroid child is overstimulated, overenergetic, often extremely excitable, readily irritated. So is the child with excessive action of the adrenal medulla or of the posterior pituitary.

This adrenal function is of the greatest importance during this period of development, not only because it is essential to good health, but because it acts on the development of the sex organs and is of tremendous importance in determining the reactions of the child as expressed by its emotions. An underactivity of the adrenals is responsible for languor, tired feeling, asthenia. It is ofttimes hard to determine whether we are dealing with a diminution of adrenal secretion or a diminution of thyroid secretion, or a diminution of other secretions in combination—or whether one, two, three, or more glands are deficient at the same time. But the adrenal function is of the greatest importance at all periods of life, and its workings should be especially studied in children and in the young because it seems to be beyond the possibility of doubt markedly related to the emotions of anger and fear; and of all the detrimental influences of life, especially in the life of the child, the element of fear plays the greatest part.

Some children are not easily frightened; others are more readily frightened, and others are of an extremely fearful or

fearsome nature; and to call these neurotic or psychopathic, and to say that they have inherited these conditions may be only too true, but it explains nothing which the parents can understand and hope to correct; nor do these terms imply in the least that the physician recognizes that there is something wrong which may be corrected. The parents must and should do everything with all children to avoid inculcating fear, and should remove any element of fear as much as possible from the mind of the child; at this age fears, though not remembered as having been experienced earlier, may persist as sensitive paths and continue throughout the whole life of the affected individual.

The adrenals consist of two parts, the cortex and the medulla. The medulla—which gives us adrenalin—responds to a stimulus associated with the emotion of fear, and the medulla plus the cortex responds to the emotion of anger. It is the adrenal cortex response which changes an emotion calculated to be expressed by fear into an emotion expressed as anger. Therefore, children with a badly balanced adrenal system, whereby the medulla area responds to stimuli without a corresponding response on the part of the cortex, are the children who are afraid, fearful, excitable, and nervous. Therefore, in young children slow growth, slow mental development, lack of energy may be dependent upon the failure of proper activity on the part of the pituitary, or the thyroid, or the adrenals, or upon a combination of these, and the overexcitable, nervous, neurotic, masturbating, easily frightened children may have too much stimulation by the thyroid, too much stimulation by the adrenal medulla, or by the postpituitary, or by all. Of course the thymus and especially the parathyroids are of the greatest importance.

Among these glands the thyroid is associated with the development of the genitalia; so is the pituitary; so are the adrenals; and if these glands which are associated with the development of the genitalia should at any period overact along these lines the child is unconsciously affected and feels a sense of attraction toward the sphere of the organs which are stimulated. This is the explanation for the slighter or greater tendency to what are called manipulations by the fingers of the organs known as the

genitalia. This is frequently only a passing phase, manifesting itself at different periods of life, according to the degree to which the endocrine system is stimulating the growth of these structures. It may occur in the early years; it may occur during the period preceding the onset of menstruation; or it may occur at any later period of life.

The thymus gland has a tremendous effect on the type of the physical and bony growth of the individual. It also stands in relation to the development of the sex organs. Its physiologic retrogression takes place in the early years, previous to which time it has inhibited too early the development of the sex structures, and so permits the sex organs to begin or continue their proper growth. Hence the too early removal of this inhibition starts an early development of the genitalia, related as they are and dependent as they are for their trophic support on the ovary, the pituitary, the adrenals, and the thyroid. A too late removal of the thymus from the sphere of activity inhibits the development of the genitalia and likewise must interfere with that normal phase of the pituitary, thyroid, and adrenal activity which is exerted on the genital sphere. In conjunction with the thyroid and the other glands the thymus and the parathyroids are likewise concerned with calcium and bone metabolism, and so the type of body form and bone development may be markedly influenced by a persistent thymus action or by too early removal of same.

As the ovaries begin to show the added secretory power, which results eventually in menstruation and ovulation, a relatively new secretion, the corpus luteum, with added power of the interstitial area, also is brought into the circle of endocrines, and all of them are now concerned with the development of the body, mind, sex organs, and sex functions—from puberty, through adolescence, to adult life.

We might imagine a family of, say ten, acting harmoniously and in concert for years. We might then picture a new member introduced into this family circle. If he fits in well with the other ten and their relations are harmonious there is a peaceful, contented, stable relationship, since they all act in concert.

But if the new member is not in harmony with the others, and is arrogant and dominant, an element of irritation and stimulation is introduced which will rouse and irritate all the others; or irritate some and depress others, and there is a resulting lack of harmony and co-ordination.

So it is with the action of the endocrine chain at the period of puberty and on through adolescence. The more stable and harmonious the activity and interrelation of the other endocrines, the more does the girl develop her menstruation without annoyances and the more certainly does she go on through the next succeeding years with little or few untoward manifestations. The more unstable or easily affected is the endocrine chain, the later and more irregularly does menstruation develop, with pain and discomfort; and the more are the other glands overstimulated or understimulated, with a resulting sense of nervousness, instability, asthenia, excitability, and all the other terms used to describe the unfortunate adolescent young.

If there is a marked hyperthyroidism, the girl will suffer from tachycardia, palpitation of the heart, excitability, and nervousness at various times. If there is a hypothyroidism, the opposite is to be expected and will surely be noted.

If there is an excessive action of the posterior pituitary, she will suffer from dysmenorrhea; her tenderer emotions are more easily aroused, blushing is noticeable, and the sex feeling—vague though it may be—or the sex instinct is more pronounced. Psychic fears are more evident.

If, on the other hand, the posterior pituitary is underactive, there may be no pain at menstruation, the menstruation may be scanty, and the girl is liable to be stout or adipose—totally different in many of her functions and appearance from the girl with posterior hyperpituitarism.

If there is a predominant stimulation of the adrenal medulla, there will be nervousness, irritability, sensitiveness, blushing, fear, anxiety, etc. If the adrenal cortex is overstimulated, the girl will show some of the characteristics of the male in the way of courage, absence of fear, decided fondness for manly ports, and, though feminine in other ways, may be less sentimental.

All these innumerable variations of interglandular relations, and they are almost limitless, give us such a variety of symptoms and types of girls that there can no longer be any attempt to apply terms to any of them except as they apply directly and specifically to each and every individual viewed as an independent entity.

The girl at school or college with a good thyroid and a good anterior pituitary is not only studious and bright, but has a more mature type of mind and is more settled than is the child with a good thyroid, but a poor anterior pituitary. The latter may be happy and gay or excitable, may have admirable qualities in other ways, but she lacks the studious, sedate, and settled character—the lack of which, however, is by no means to be considered a disadvantage at this time. And so girls at the school or college age manifest different tastes and likings, varying emotions, varying dispositions, according to their endocrine make-up; and it is essential for parents and educators to understand these facts, for it is absolutely true that while education, training, and environment have a most marked effect on the emotions, disposition, and character, the endocrine make-up, the endocrine activity, and the endocrine interrelations are the decisive factors.

Therefore, this period of puberty and adolescence or, rather, the entrance upon this stage of puberty is as much a change of life for the growing girl, leading up to and preparing her for the activities of the next thirty years, as is what the laity call the "change of life" which occurs most frequently in the late forties; and the parallel between the symptoms at this stage and the symptoms at the later "change of life period" is most marked. But here we are dealing with the excitation of activity of these glands, whereas at the climacterium we are dealing with the stage of retrogression. And very often, as the woman goes into this adolescent period peacefully or calmly, or upset and disturbed, so she may go out of it in the same way.

It must be remembered, however, that this would be more uniformly true where it not for the innumerable factors and complications of the period between adolescence and the true

change of life—for here come in the questions of marriage, childbirth, miscarriage, nursing, operations, infectious diseases, fortunate and unfortunate environment, happiness or unhappiness, mental shocks and worries, the responsibilities and cares of motherhood, all of which contain vast possibilities in the way of a fortunate or unfortunate effect upon any one of the important endocrines or on the whole system.

Some endocrine chains are so stable that none of the abovementioned factors disturb them or effect them permanently. Other chains are so sensitive or unstable that they are more or less profoundly affected by what often appears unimportant. Certain families are characterized by marked stability of endocrine relationship, and in many families one or other of the glands is so dominant that it characterizes practically every one of the descendants for generations for either good or bad. Therefore, marked mentality and stability of character, probity, and high sense of morality characterize certain families for generations—nervousness or irritability, or a tendency to "neuroses" and psychoses" and varying degrees of what are called emotional states may characterize other families.

If, for instance, the pituitary is the dominant gland, a vast majority of the descendants for generations may be of tall or powerful stature, or of strong able minds—though it is to be well understood that intermarriage with other endocrine types is liable to modify this type of ascendancy. If a family is characterized by pituitary instability, the father or mother may be acromegalic in body type, yet some of the children may show evidences of overactivity of the anterior pituitary, while others show evidences of underactivity. If thyroid instability is the characteristic, some of the descendants will lean toward a hyperthyroidism or various grades of Basedow's disease, while others will tend toward hypothyroidism or various grades of myxedema. Families characterized by hypersensitiveness and overactivity of the posterior pituitary, the adrenal medulla, are likely to show "neurotic" types and various grades of psychoses and neuroses. Accordingly, if we could have the photographs and the history of our patients' ancestors we would find every normal or

abnormal state dependent upon endocrine activity to have been inherited, though often in forms apparently unrelated, but actually, as our knowledge grows, due to the same endocrine aberrations.

The period of regression, at what is known as the climacterium, means a rearrangement of the gland activities, a down hill, as it were, since the function of child bearing is passing. The ovary is supposed to pass out of the sphere of action just as at puberty it entered into a new sphere of action; and if the other glands regress in equal and parallel ratio and the interrelation between the glands is preserved, then the individual goes through this trying period with few if any manifestations of an annoying character. But if the rearrangement is not a normal or stable one, if some of the endocrines regress more quickly than they should and others more slowly than they should, or if only the ovarian activity regresses and most of the others do not, we have all the innumerable possible variations and symptoms due to hyperactivity or hypo-activity, or combination of hyper- and hypo-, involving the anterior lobe of the pituitary, the posterior lobe of the pituitary, the thyroid gland, the adrenal cortex, the adrenal medulla, the ovarian interstitial gland, and the ovarian follicular apparatus. Of all the gland anomalies at this period overactivity of the posterior pituitary is productive of the largest number of physic and psychic abnormalities.

The flushes which are associated with the menopause or climacterium in many patients are due to absence of the secretion of the ovary which in conjunction with the posterior pituitary (for these two glands are practically sisters in the family) preserves a normal vasomotor balance. If the ovaries regress or are removed and the postpituitary persists in its former degree of activity or its activity is increased, then the flushes are extremely marked. If the adrenal medulla is overactive the flushes are still worse. The administration of ovarian extract and ovarian residue therefore helps many patients and cures some, but does not cure all by any means. This is due to the fact that the pituitary, freed of its association with the ovary, and the adrenal medulla are responsible for the flashes or flushes, and unless to the ovary be added some gland extract which inhibits and holds

the posterior pituitary and adrenal medulla in check, only a certain amount of benefit will result.

There is a difference between the term "climacterium" and the term "menopause." Menopause means a cessation of the menstruation; the climacterium means the period of transition from the most active thirty years of a woman's life to the subsequent period of peace, quiet, and freedom from menstruation and its associated annoyances. A woman may be in the climacterium period and menstruate normally or even excessively. She may, therefore, have some or other of the "change of life" symptoms long before menstruation ceases, and the annoyances may persist for months or years after the menopause. It is most important to recognize this all too true state of affairs, for only then can a proper interpretation be made and proper therapy instituted. And after the menopause and climacterium are passed there are still possible the various hyper- and hypo- annoyances involving the endocrine chain, and therefore this is the period when marked neuroses and psychoses (due to the endocrines) may develop, just as in the adolescent stages there are various neuroses and some of the psychoses—the most important of the latter being dementia præcox.

One all-important observation should not be left out of consideration, for it is a most valuable aid to diagnosis at any stage of the active period of life—the way the patient reacts a few days before each menstruation. This is a sign-post indicating which one or more of the glands is sensitive to over- or under-stimulation. Many girls and women never know before each period that they are to menstruate; others suffer from physical pain; and many suffer from nervous and psychic reactions of a character unusual to them in the intermenstrual period. A girl or woman may be perfectly well for the three weeks following menstruation, and then for a week, or it may be for only a few days, may be depressed or excited, irritable or extremely nervous, restless, "crazy," as some describe it, full of restless energy at this time, though calm, peaceful, or even lazy at others. Here it is our obligation and duty to put our finger on the gland or glands which are over- or underworking, for such symptoms point to an

instability in the chain, and no physician should neglect to characterize these symptoms as of the greatest importance not only for the therapy to be instituted, but as indicating the latent possibilities for subsequent magnified upsets of this or other glands. The one thing which medical men, and especially the gynecologist and also the physician who treats children and young girls, must do is to remove from his vocabulary the words "neurotic," "neurasthenic," and "hysteric," for they are only cloaks for ignorance and make a very bad impression on the parents and on the child or girl concerned. Practically all these types cover deviations due to the endocrine aberrations, and if treatment were instituted sufficiently early, especially during childhood, and more attention were paid to stimulating body and mental growth by endocrine therapy and to correcting states of excitability, fear, etc., by the same methods, the effect on the succeeding years of the affected individual's life would be so markedly for the better that I am sure the future will find us astonished at the possibilities of such therapy during these vital and all-important years.

CLINIC OF DR. H. WESSLER

MT. SINAI HOSPITAL

THE DIAGNOSIS OF ENCAPSULATED PLEURAL EFFUSIONS

IN the study of pleural effusions it is customary to place the major emphasis on the free effusions and to reserve for minor consideration those which are encapsulated.

This involves the tacit assumption that the former represent the usual and typical forms and that the latter are unusual and exceptional. Yet it may be doubted whether this assumption is altogether justified and whether pleural effusions are not more often sacculated than is commonly believed.

The pleural cavity is a complicated potential space in which, from purely physical causes, fluid may readily be walled off. Given an inflammatory process in the pleura, adhesions will be most apt to form in those regions in which the movement of the lung and chest wall are restricted. An exudate in the pleural cavity accumulates first in the lower and axillary portions and here the movement of the chest and the lung is greatest. The mesial and apical portions, on the other hand, have the least movement in respiration, and for this reason adhesions, excluding the effusion from them, are oftenest found in these locations.

Further, it requires but a glance at the complicated arrangement of the lobes and fissures, with the numerous points of reflection of the pleura at the diaphragm, mediastinum, and the fissures, to realize the opportunities that are afforded for the isolation of fluid in the numerous recesses which are thus formed.

What are the conditions which favor the encapsulation of effusions?

Undoubtedly of major importance is the element of infection. Transudates are rarely sacculated; exudates, on the other hand, frequently are. Evidently this is because inflammation with the formation of plastic exudate will agglutinate apposing pleural surfaces and tend to localize the effusion; and it may also be remarked that the reflex immobility of the lung and chest wall will favor this tendency. Another element which may determine the localization of a pleural effusion is the existence of an inflammatory focus at the surface of the lung, the slow extension of which to the pleura may result in an encapsulated effusion.

We are, therefore, in our discussion of this subject practically limited to effusions of inflammatory origin—whether these are acute, purulent, and pyogenic; or, on the other hand, chronic, non-purulent, and tuberculous.

I should now like to present to you a number of patients who illustrate the various types of encapsulated effusion. If in my presentation I shall seem to emphasize their topographic features, it will be because the problem which confronts us in these cases is not so much the determination of the existence of an effusion, but rather its exact localization, in order that aspiration and subsequent operation may be performed with the greatest precision. In order to present this subject with some attempt at a systematic arrangement I have divided encapsulated effusions, in respect of their location, as follows:

1. Effusions encapsulated in the general pleural cavity (parietal effusions).
2. Effusions encapsulated between the lung and the diaphragm.
3. Effusions encapsulated between the lung and the mediastinum.
4. Interlobar effusions.

1. EFFUSIONS ENCAPSULATED IN THE GENERAL PLEURAL CAVITY

I wish to present first a patient who illustrates perhaps the most common form of encapsulated effusion, that is, one situated

in the axillary portion of the chest. The important facts in his history are as follows:

Case I.—The man is twenty-four years of age, and for three weeks suffered with remittent fever, cough, and at times a moderate mucopurulent expectoration. These symptoms were consequent upon a pneumonia three weeks previous. He presents the appearance of acute illness, is somewhat dyspneic, and has the pallor of a mildly septic individual. He shows the following physical signs: moderate dulness over the outer two-thirds of the right chest, most marked at the base. There is also flatness at the right apex and in the upper part of the right axilla. In the upper portion of the chest the breathing is tubular; at the right base the breathing is diminished; and along the border of the dull area in the mesial half of the chest there are numerous subcrepitant râles. The mesial half of the chest presents normal auscultatory sounds.

The physical signs evidently point to a collection of fluid which is situated in the apical and axillary portion of the right chest, extending somewhat anteriorly and posteriorly. This patient was aspirated posteriorly in the eighth interspace—that is, at the conventional point—and no fluid was found. Being convinced of the presence of fluid, the needle was then inserted in the lower right axilla, and thick pus was obtained. On operation there was found a collection of pus in the axillary portion of the chest corresponding to the physical signs of effusion, being walled off firmly anteriorly and posteriorly. The empyema cavity was composed of two loculi, one above the other, communicating by a narrow passage (Figs. 2, 3).

We have illustrated here one of the common sites for the encapsulation of empyemas, which form most readily in the axillary portion of the chest and may extend anteriorly or posteriorly for a variable distance. As may be expected, the physical signs are frequently very puzzling. It is especially to be noted that in the presence of an axillary effusion which extends to the posterior aspect of the lung the entire anterior portion of the chest may present a loud tympanic note on percussion.

At this point I cannot do better than discuss with you some

points in regard to exploratory aspiration of the chest in these cases. In general, we aspirate over an area of marked dulness or flatness, avoiding the costophrenic sinus where the pleural cavity is shallow, and also the mesial portion of the chest where we are more apt to encounter uninvolved pleura or adhesions

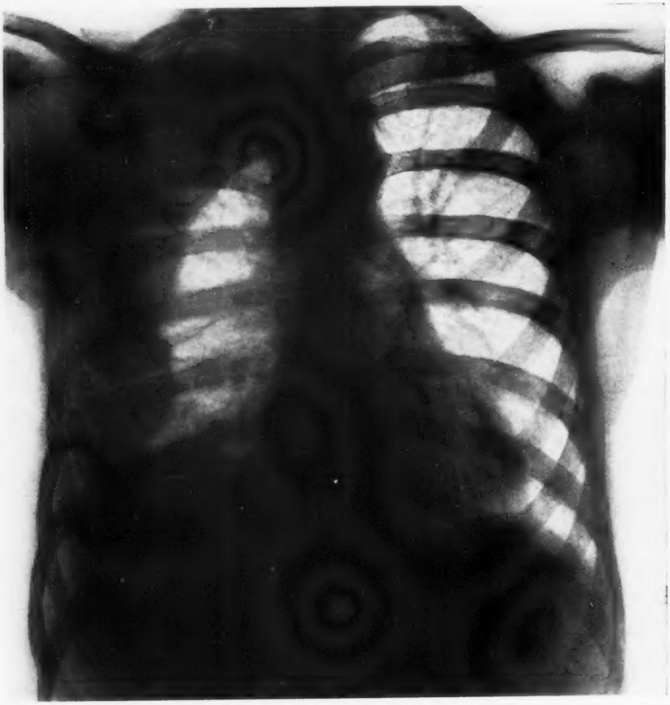

Fig. 2.—Case I. Bilocular axillary empyema.

about the fluid. Yet even when we observe these precautions and aspirate in the common locations, such as in the scapular line, it is surprising how often a dry tap is obtained. A lung which is atelectatic, due to compression. or one covered by plastic exudate may produce the same dulness as fluid, especially when the latter is not present in large amount. For this reason if the

first aspiration is unproductive it is wise at once to insert the needle nearer the center of the area of dulness in order that the margin of the effusion may be avoided. The repeated unsuccessful aspiration of a chest in a small area posteriorly cannot be too

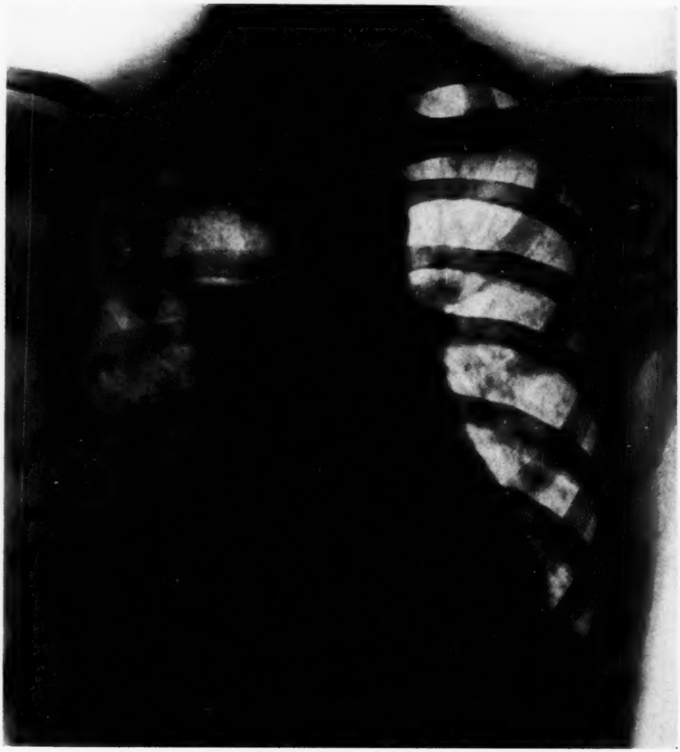

Fig. 3.—Case I. After operation. Secondary mesial pyopneumothorax.

much deprecated. Having in mind the frequency of axillary effusions and the great depth of fluid in this region, I have been impressed with the advisability of aspiration in the axilla in cases of atypical effusions. If one aspiration behind is unsuccessful, it is wise at once to insert the needle in the anterior or posterior

axillary line. With one puncture the needle may be pushed either anteriorly or posteriorly, or up or down, for a variable distance, and usually pus will thus be found. In fact, it is surprising in how many cases of encapsulated pleurisy aspiration in the anterior axillary line, the height depending on the physical signs, is at once successful; nor need we have any fear of injuring important structures in this region, as the aspiration here is quite as safe as posteriorly.

In the diagnosis of this, the commonest type of encapsulated effusion, it is worth while to emphasize one of the cardinal physical signs which distinguishes it from a free effusion. As you are aware, when fluid accumulates in a pleural cavity which is free from adhesions, its upper level, under the influence of the intrapleural pressure and the elastic force of the lung, assumes a characteristic curve. This curve, which it is assumed corresponds to the upper limit of flatness, begins at the spine, at a variable height, and ascends obliquely upward to reach its highest point in the axilla, whence it descends anteriorly to the base. The presence of encapsulating adhesions in the pleural cavity will so interfere with the operation of the intrapleural tension that this characteristic curve will be altered and the area of flatness will have an unusual conformation. Of the greatest significance will be an area of resonance in the mesial portion of the chest, parallel to the spine and extending for a variable distance from it. Instead of an oblique upper level of fluid, this level may actually be perpendicular or nearly so. I can best illustrate this point by presenting the following case:

Case II.—This girl, ten years of age, has had fever, cough, and pain in the right chest for five weeks. She has not been acutely ill, but has gradually lost considerable weight. When you examine her chest posteriorly you will observe that the mesial third is resonant. In the outer two-thirds there is marked dulness from the apex to the midscapular line, increasing in intensity to the base, where the note is flat. The breathing at the apex is diminished; in the middle third it is bronchial, and at the base it is absent. Aspiration was performed in the lower

axilla, and clear fluid, containing 100 per cent. lymphocytes, was removed. We are dealing presumably with a tuberculous effusion which is encapsulated in the axillary region of the right chest. A study of Fig. 4 must convince you that a collection of fluid could not maintain such a vertical position were it not supported by adhesions.

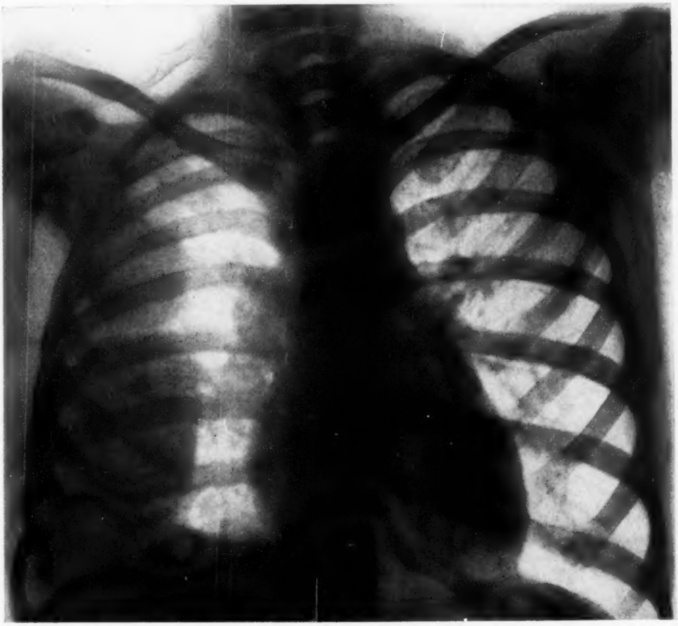

Fig. 4.—Case II. Encapsulated axillary effusion, tuberculous. Mesial half of chest uninvolved.

I would now like to present to you a few cases which illustrate the various sites within the chest which encapsulated effusion may occupy. These sites are often determined by the situation of an underlying inflammatory process in the lung, which is directly responsible for the effusion. In other cases, as in those which are due to metastatic infections of the pleura from foci elsewhere in the body, the localization cannot be thus explained.

Empyemas limited to the region of the upper lobe are not common. They may be secondary to an upper lobe pneumonia, but not necessarily so. In view of the greater frequency of pneumonia of the lower lobe, it is likely that they are more often secondary to a pneumonic process in the upper portion of the lower lobe, and they may, therefore, as they extend surround the upper lobe and appear to originate from it. Naturally, from the unusual location of the physical signs, empyema may not be suspected for some time, and this is particularly true in children, in whom the signs of pleural effusion may closely resemble those of consolidation.

Case III.—Observe this child, six years of age, who four days before admission to the hospital became ill, with pain in the right chest, fever, and cough. At that time the physical signs were as follows: Right posterior dulness from the midscapular region to the base, with bronchial breathing and many redux râles. The dulness extended into the axilla. White blood-cells, 49,800; polynuclears, 71 per cent. Evidently there was a pneumonic process, in the stage of resolution, of the right lower lobe. Note that there was no evidence of disease in the upper lobe. Six days later the temperature was still 103° F., and at that time there developed dulness and bronchial breathing anteriorly and posteriorly over the right upper lobe region. Four days later the physical signs were as follows: Dulness from the apex to the angle of the scapula, with bronchial breathing and voice, and with a moderate number of fine râles. For four days longer there was continued fever. At that time the Roentgen examination showed the appearance in Fig. 5, which indicates a large effusion occupying the upper two-thirds of the right chest.

This child was operated upon, the incision being made at the fourth space in the axilla, and one pint of thick pus was obtained. The lower third of the pleural cavity was uninvolved.

Although in their earliest stages apical empyemas will offer difficulties in diagnosis, there are certain distinctive signs which develop later which we can utilize in distinguishing them from an upper lobe pneumonia. The limited space in the apical region

can accommodate only a small amount of fluid. For this reason as the effusion increases in size it has a tendency to rupture its limiting adhesions and to involve the dependent parts of the pleural cavity. This is graphically shown in the plate of the case I have just presented to you (Fig. 5), in which you will notice a faint narrow shadow in the right axilla extending from the effusion toward the base. There is little doubt that if left to itself the empyema would soon have involved the entire chest.

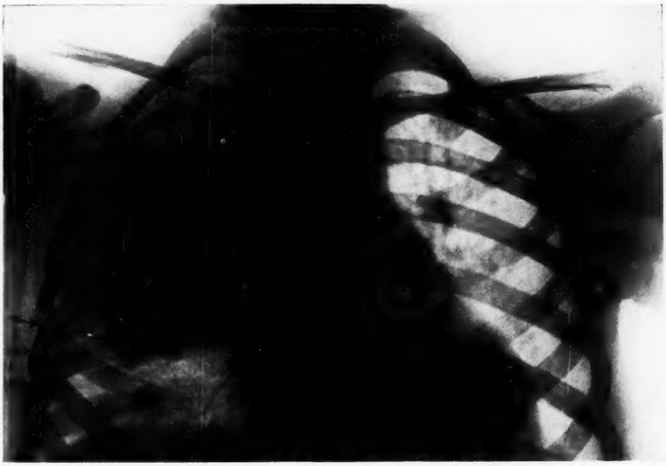

Fig. 5.—Case III. Empyema in upper half of chest. Note shadow in lower axilla, indicating beginning involvement of the general pleural cavity.

Case IV.—On the other hand, a sequence of events just the opposite of that just described may be observed. The child before you became ill one week before admission with cough, fever, and sharp pain in the right lower chest. At that time the physical signs indicated a pleural effusion limited to the posterior and axillary regions, with no involvement of the upper lobe region. Anteriorly, hyperresonance. During the next two weeks we were able to follow the gradual extension of the effusion upward to the apex on the posterior aspect of the chest. On operation there was found an empyema cavity in the posterior

and axillary regions, divided into an anterior or axillary part and a posterior part by a ridge. The lung anteriorly was freely movable. The cause of the empyema was a cortical lung abscess which had ruptured. The prolongation of the empyema down-

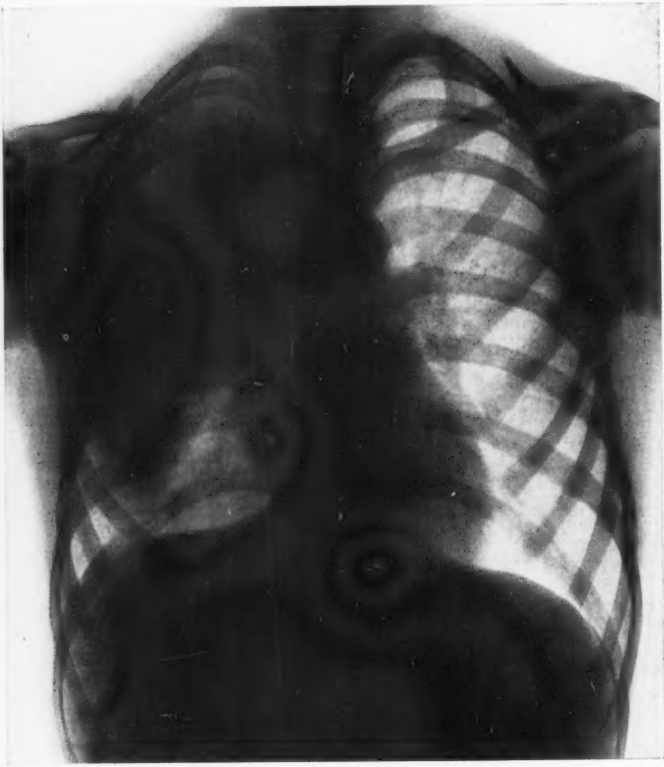

Fig. 6.—Case IV. Empyema encapsulated in upper two-thirds of chest. Occupies the axillary and posterior portions of pleura.

ward toward but not quite to the base is clearly indicated in Fig. 6.

I should therefore like to emphasize, in distinguishing an upper lobe effusion from a pneumonia, the importance of the develop-

ment of an area of dulness or flatness in the axilla, especially when this increases from day to day. We have, moreover, in the Roentgen plate a very accurate and early means of making this distinction.

More common than apical empyemas are those which are encapsulated at the base—here again usually secondary to a lower lobe pneumonia. Once more, the location of the physical signs—

Fig. 7.—Case V. Left basal encapsulated empyema. Note displacement of heart and trachea to the right.

which may be coextensive with the lower lobe—will make it very difficult to distinguish between a pneumonic process which is persistent and an effusion. In both of them the upper limit of dulness may be horizontal. The breathing may be various, depending on the amount of fluid and on the mobility of the underlying lung. There may thus be either bronchial breathing or bronchovesicular breathing or diminished breathing. The

greatest difficulty occurs in those cases in which the presence of thick shaggy exudate along the margin of the effusion gives rise to râles of all sizes and intensity. Here the difference between a pleuropneumonia with slow resolution and an encapsulated empyema may keep the examiner in doubt for some time—a doubt which is often only resolved by exploratory aspiration.

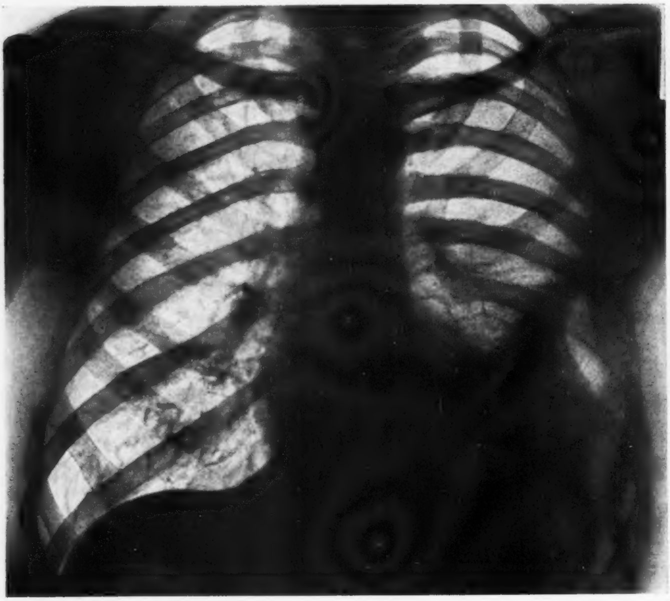

Fig. 8.—Case V. After operation, showing adhesions in axilla. Note recession of heart and trachea to normal position.

Case V.—A case of this type is illustrated by another plate (Fig. 7). This patient is forty-five years of age, and has had the usual symptoms following pneumonia, which arouse the suspicion of a pleural effusion at the left base. You will note from the plate the location of the shadow, which is typically that of a pneumonic process, yet the physical signs left one in doubt between a pneumonia and an effusion. In the next plate (Fig.

8), taken after operation, you will note the area of pneumothorax remaining after the evacuation of the fluid and the thickened adherent lung along its margin.

CASE VI.—In other cases of exclusive involvement of the axillary half of the base of the lung the sharp limitation of the area of dulness, both mesially and above, makes the distinction

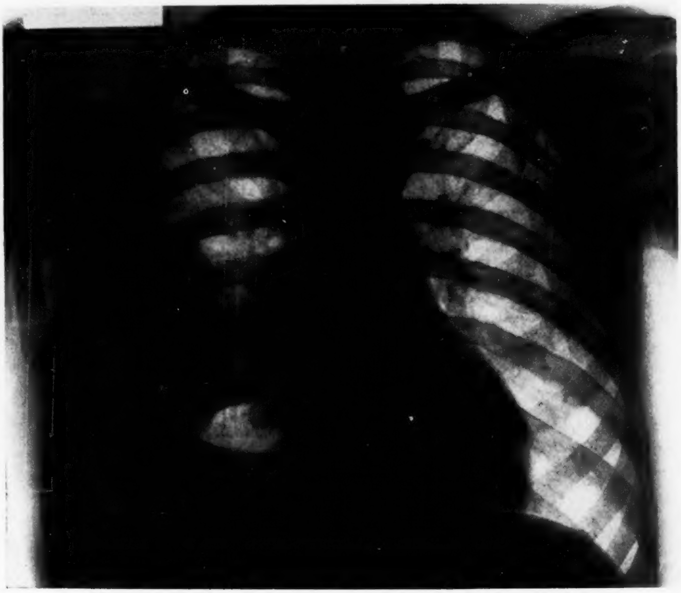

Fig. 9.—Case VI. Encapsulated basal empyema due to perforated lung abscess.

from pneumonia an easier one. Such a case is illustrated by this plate (Fig. 9), in which you will observe a well encapsulated effusion which occupies the lateral half of the right lower chest. In this case the patient presented an empyema of some weeks' duration, which followed the rupture of a superficial lung abscess.

I shall now call to your attention a very unusual location for an effusion encapsulated within the general pleural cavity, that is, in the mesial portion of the chest near the mediastinum. As a primary effusion this is perhaps the rarest form. It is more often seen as a secondary collection which occurs occasionally after operations for the evacuation of an empyema. Frequently this portion of the chest is protected by adhesions, so that pus

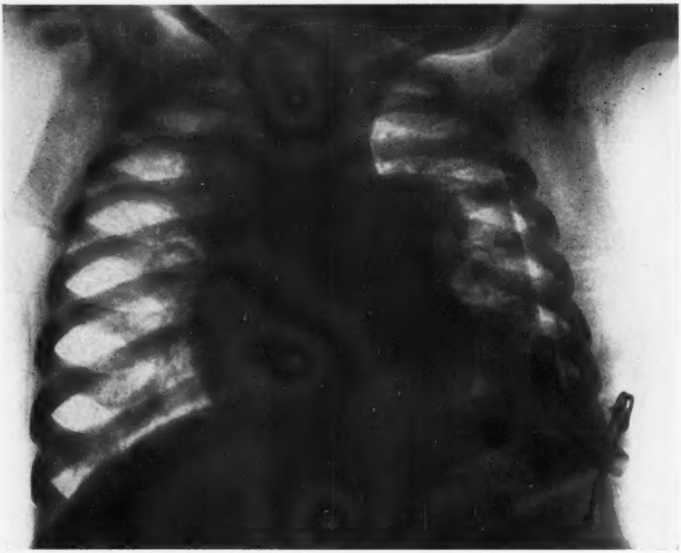

Fig. 10.—Case VII. Mesial empyema, postoperative.

does not collect in it. If, however, during the course of the operation these adhesions are severed, and this portion of the cavity becomes infected, and effusion may form in this location which, owing to the adhesions, is not readily drained, and may, therefore, give rise to urgent symptoms. These effusions are particularly difficult to recognize by means of physical examination because the altered physical conditions in the chest which result from the operative pneumothorax tend to obscure them.

We are, therefore, usually dependent on the Roentgen examination for the discovery of this type of empyema.

Case VII.—This type of empyema is illustrated by a patient two and a half years of age whom I observed recently. The salient facts of his history are as follows: Cough, fever for thirteen days, with physical signs on admission of a large pleural

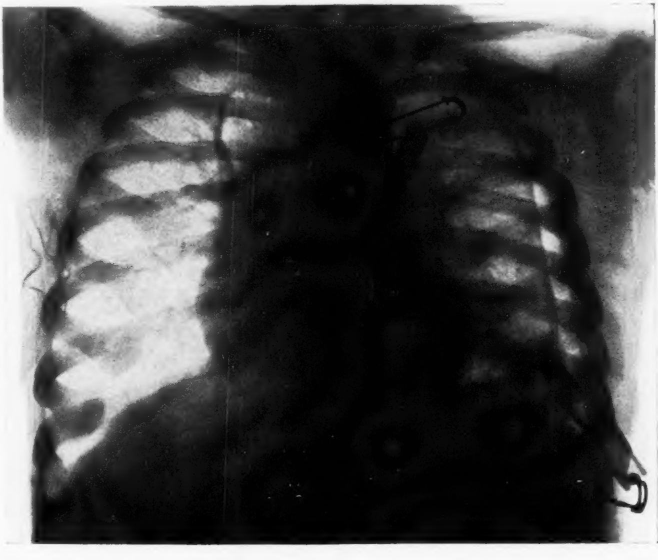

Fig. 11.—Case VII. Mesial empyema, drainage-tube at site of previous effusion.

effusion in the left chest, from apex to base. Aspiration disclosed greenish pus which contained Staphylococcus aureus. A minor thoracotomy was performed posteriorly. In spite of drainage the high temperature continued for four weeks. Examination of the patient in order to determine any possible retention of pus showed an area of dulness which extended along the left border of the heart, in the second and third interspaces. You will note on the plate (Fig. 10) a circular shadow near the upper

mediastinum on the left side, which is due to a small collection of fluid encapsulated in this region. An intercostal incision was made at this point and 2 ounces of fluid were evacuated. A subsequent plate (Fig. 11) shows the drainage-tube at this point, with a disappearance of the shadow.

It may be profitable to pause in our discussion and re-examine in the light of a few illustrative cases the terminology which we have thus far employed. I refer to the terms "encapsulated" and "localized," which, although frequently synonymous, are not necessarily and always so. In the cases so far presented to you the effusion was encapsulated by adhesions and also localized to a definite and at times a small area in the pleural cavity. On ther other hand, I have to call your attention to an unusual group of cases in which a pleural effusion occupying a large part of the pleural cavity may be so subdivided by septa that a number of adjacent loculi are formed which may or may not communicate with each other. It must be clear to you that under these circumstances the effusion, although encapsulated, may not be localized, and that the physical signs produced by the adjacent collections of fluid may differ in nowise from those of a large free effusion.

Case VIII.—Perhaps the simplest form of such an encapsulated effusion without localization is illustrated in Fig. 12. In this case, which was one of hydrothorax associated with nephritis in a child, only the x-ray plate revealed the unusual double curve, which represents the upper level of the fluid anteriorly. An adhesion, probably in the region of the interlobar fissure, has divided the pleural cavity into two halves, in each of which the normal intrapleural forces have come into play in such a way as to reproduce in miniature two S curves which merge into each other.

Much more complicated are the cases of purulent effusions of this type with two or more sacculations. The circumstances under which these cases come to light are of interest both to the clinician and to the surgeon. Frequently the possibility of multiple pockets of pus is only considered after a period of con-

tinued fever following operation. Thoracotomy may have been performed and for some days pus has flowed copiously from the drainage-tube. A day comes when drainage ceases, yet the fever persists and the condition of the patient is aggravated. The case may appear to have been one of simple empyema, with a chest full of pus. None the less, in spite of apparently efficient drainage, the physical examination will reveal an area of flatness, often in the upper portion of the chest, which can be due only to

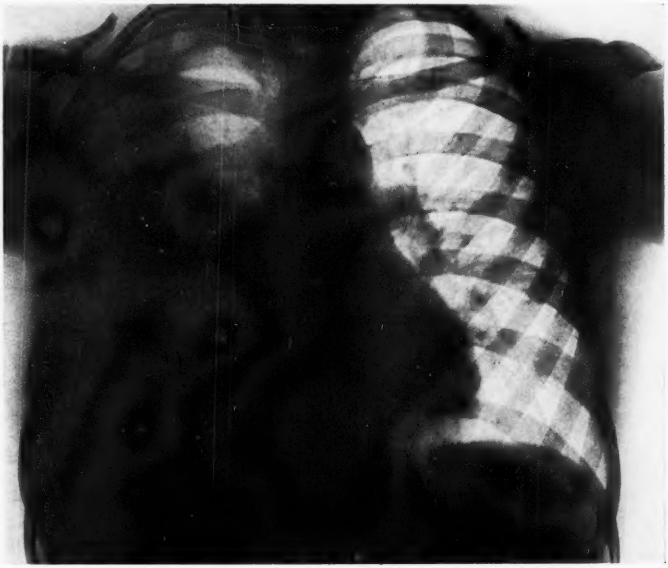

Fig. 12.—Case VIII. Sacculated hydrothorax showing two oblique upper levels.

undrained, encapsulated pus. Such a sequence of events is illustrated by this boy whom I present to you.

Case IX.—You will observe that he has two drainage-tubes in his chest, one low down on the right side posteriorly, and a second just below the angle of the scapula. A considerable amount of pus has been evacuated through these openings, yet

he remains very ill. You will observe that the upper part of his right chest is abnormally prominent. If you percuss his chest you will find marked dulness from the apex to the level of the sixth rib posteriorly with an absence of breath sounds. Anteriorly, on the contrary, the note is hyperresonant, almost

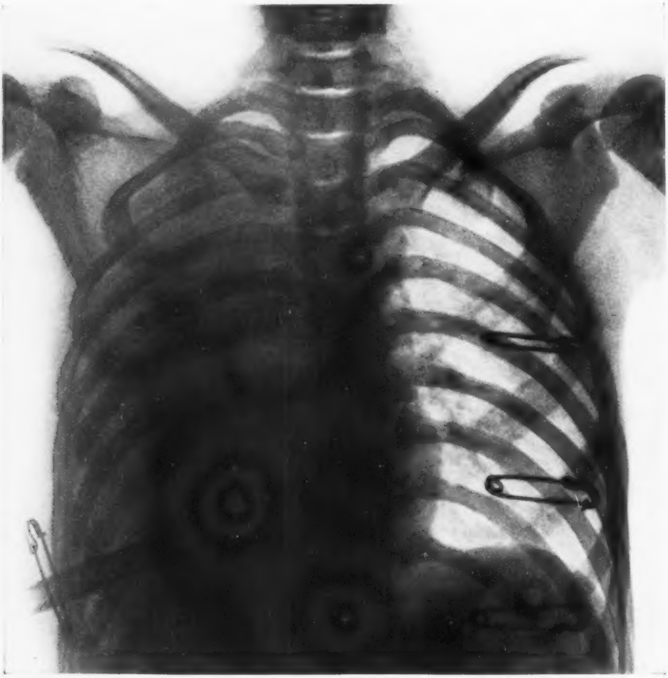

Fig. 13.—Case IX. Generalized pleural effusion with three sacculations. Drainage-tubes in two lower loculi. Retention of pus in apical collection. Note separation of upper ribs.

tympanitic, the breath sounds are harsh and the transmitted voice has a nasal quality. We must interpret these signs as those of fluid on the posterior aspect of the right upper lobe, fluid which is under considerable tension and is compressing the upper lobe backward and not communicating with the lower sacculations.

And, in fact, we have already performed an exploratory aspiration posteriorly and pus has been obtained. If you will study his x-ray plate the condition of affairs will be graphically revealed to you, and I would call your especial attention to the marked separation of the ribs over the upper lobe region (Fig. 13).

You have here presented the surgical aspect of these cases and some of the problems they offer for solution. No less interesting problems occasionally confront the internist, and their solution may throw instructive light on the manner in which these effusions arise in the chest. The different sacculations in a multilocular effusion do not of necessity develop simultaneously. For this reason, depending on their age, the character of their contents may vary. The fluid in one loculus may be frankly purulent, whereas an adjoining one may be clear and contain few or no bacteria. In other words, a localized collection of pus, even when it is completely walled off, may give rise in its vicinity to a pleurisy which is at first aseptic, although its cytology is already polynuclear. The clinician examining such a case will usually obtain only the physical signs of a large pleural effusion, and if he is unfortunate enough to aspirate over the region of the aseptic pleurisy, the encapsulated purulent collection will escape him.

Case X.—I can best indicate the problems which arise here by presenting this young woman, who for one week has had high fever and pain in the right chest. The physical signs were those of a large pleural effusion in the chest, which, because of the symptoms and the characteristic blood count, was naturally presumed to be purulent (Fig. 14). It was therefore a cause for surprise when on aspiration of the lower portion of the chest clear fluid was obtained. Examination of the fluid, however, showed the presence of over 90 per cent. polynuclear cells; culture was sterile. Such an aseptic polynuclear pleurisy must have as its basis one of two causes, either an inflammatory process near the surface of the lung, such as a lung abscess or an encapsulated effusion of pus in the pleural cavity. We once more investigated the history of this patient and could find

neither history nor symptoms which pointed strongly to disease of the lung. One important fact, however, was elicited. For some weeks previous to her present illness the patient had had recurrent boils. It was determined to aspirate the chest once more, this time in the apical region, in the hope of discovering an encapsulated collection of pus. An area of marked dulness

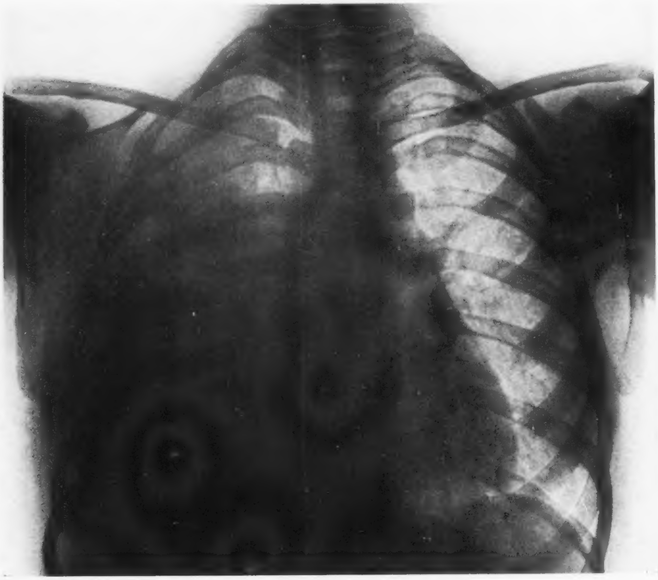

Fig. 14.—Case X. Generalized pleural effusion, apical encapsulated empyema with basal aseptic pleurisy, simulating a free effusion. Metastatic, secondary to furunculosis.

in the supraspinous fossa was selected for aspiration. At this point thick yellow pus containing Staphylococcus albus was found. Judging from the bacteriology, we had here evidently a metastatic infection of the pleura of the apex of the chest secondary to furuncles. Subsequent to this there developed an aseptic pleurisy involving the lower part of the pleural cavity.

The further course of this case is also of interest. Within

a few days the previously aseptic pleurisy became frankly purulent. It was assumed that the apical collection of pus communicated with the lower collection, and for this reason a low posterior drainage was made. That this was not sufficient soon became evident. After a temporary improvement the patient once more was ill with fever. Apparently the upper sacculation was walled off and did not drain through the low

Fig. 15.—Case X. Evacuation of lower effusion. Retention of apical sacculated empyema. Note drainage-tube at lower edge of apical empyema.

thoracotomy. If you will study the plate (Fig. 15) made at this time you will observe that the drainage-tube is arrested at the lower limit of the apical sacculation, which is not draining. After a secondary operation this residual pus was evacuated and the patient has now completely recovered.

A superficial lung abscess may also be the cause of either a purulent or non-purulent pleurisy in its immediate vicinity. I

can recall several cases in which aspiration at two different sites in the chest revealed different kinds of pus. In these cases, however, the thicker, more purulent fluid was aspirated from a superficial lung abscess and not from a sacculation in the pleura. It must be apparent to you that the distinction may not be an easy one and that your judgment will have to be based on all the data, both physical and symptomatic.

2. EFFUSIONS ENCAPSULATED BETWEEN THE LUNG AND THE DIAPHRAGM

We have thus far considered encapsulated effusions which are situated at various points between the lung and the thoracic

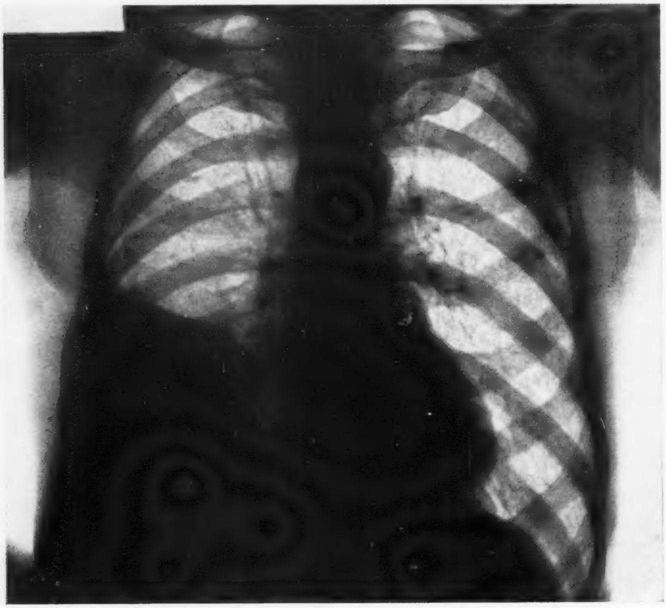

Fig. 16.—Case XI. Infrapulmonary (diaphragmatic) empyema.

walls. These may be aptly described as parietal effusions, Although their diagnosis and localization is often difficult because

of the atypical signs, the physician is aided somewhat in his search by the superficial character of the disease. In the effusions about to be described he is denied this advantage because the fluid does not lie in contact with the chest wall, but is rather enclosed between the lung and the adjacent thoracic or abdominal organs.

We will first consider the so-called diaphragmatic effusions, a term which is rather vague and is better replaced by the term

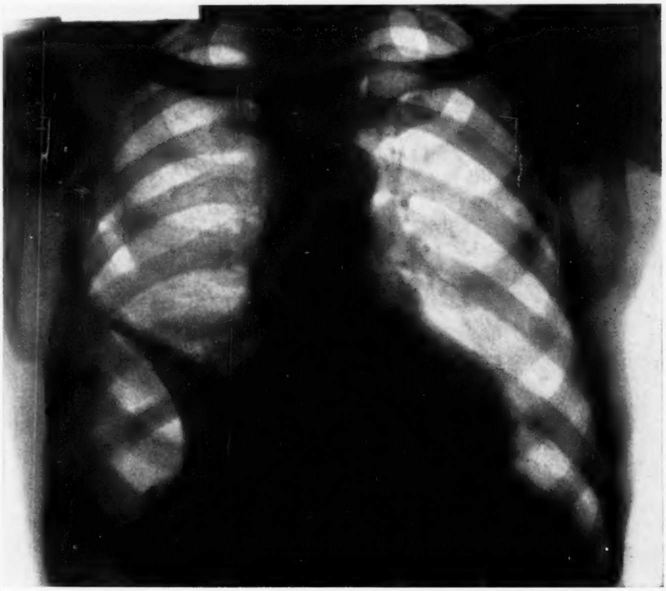

Fig. 17.—Case XI. Infrapulmonary empyema, after operation.

infrapulmonary effusion or empyema. In a case of this sort the effusion begins in that portion of the pleural cavity which is enclosed between the dome of the diaphragm and the lung above it. As it increases in size it is prevented from infecting the general pleural cavity by adhesions along the lower margin of the lung. It is evident from its position that the physical signs will be confusing; in fact, they will closely resemble those of

a subphrenic abscess, and they will be characterized by the signs of a basal fluid accumulation which are modified by those due to an interposed and probably compressed lung.

Case XI.—I may best illustrate this rather uncommon condition by this patient, who for several months has been suffering from an inflammation localized at the lower portion of his chest which gave rise to remittent fever and cough accompanied by considerable expectoration. At the right base there was an area of dulness which extended from the angle of the scapula to the base, where the note was quite flat. The upper limit of the dulness was horizontal or slightly convex. The breathing and movement of the lower chest were almost absent. At operation there was found a cavity which was limited above by the lower surface of the lung, and below by the diaphragm, which contained a large amount of pus. The general pleural cavity was unaffected. The condition found is graphically illustrated in the plates which were taken before and after operation (Figs. 16, 17).

3. EFFUSIONS ENCAPSULATED BETWEEN THE LUNG AND MEDIASTINUM

This form of encapsulated effusion, which is often misnamed "mediastinal," is perhaps the rarest of all, and the physical signs which it may produce are extremely difficult of interpretation. Too little is known of these cases to present a definite clinical picture, nor are the physical signs of sufficient distinctness to speak of them in general terms. I can do best, perhaps, by bringing to your attention two cases which have come under my observation.

Case XII.—(*a*) This young woman, who is twenty-four years of age, comes of a tuberculous family. The onset of the illness, which occurred four weeks ago, was characterized by fever, malaise and dry cough, and pain in the left chest on breathing. She was acutely ill. The physical signs at that time indicated a tuberculous process at both apices. A few days after entrance

to the hospital she developed definite signs of an effusion of moderate size at her left base, which was found on aspiration to be a sterile fluid containing 95 per cent. lymphocytes. She continued to be ill, and one week later there was noted an area of dulness on the left side along the border of the sternum in the

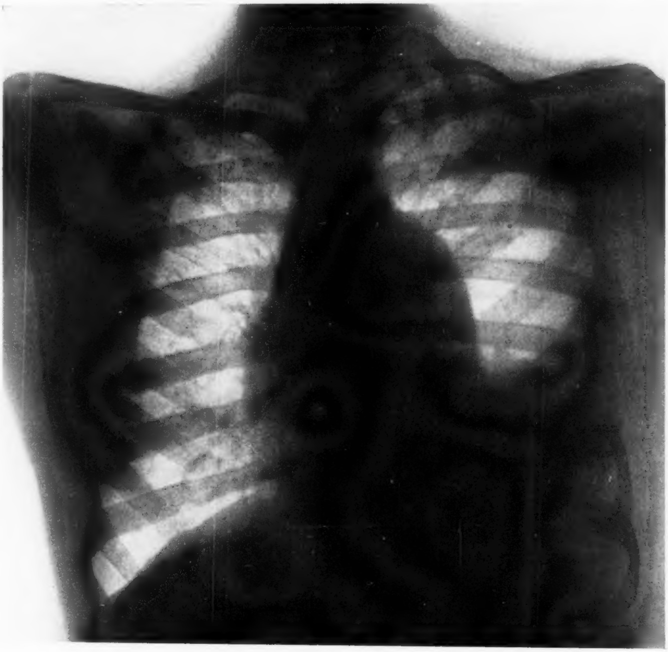

Fig. 18.—Case XII. Mediastinal effusion. Case of upper lobe tuberculosis; effusion at left base; fluid along the left border of the heart. Displacement of heart.

second and third interspaces. At this point there were, however, no breathing changes. The heart was slightly displaced toward the right side. It is hardly necessary to say that the remarkable conditions—which were only disclosed by the Roentgen examination and which are shown in the plate (Fig. 18)—were not suspected. You will observe, in addition to the evidence of bilateral

apical tuberculosis and an effusion at the left base, a homogeneous shadow which is situated along the left border of the heart apparently continuous with the heart shadow. The interpretation of this shadow was a matter of great difficulty. It was necessary to exclude mediastinal new growth, aneurysm, and dilatation of the cavities of the heart or of the aorta. The

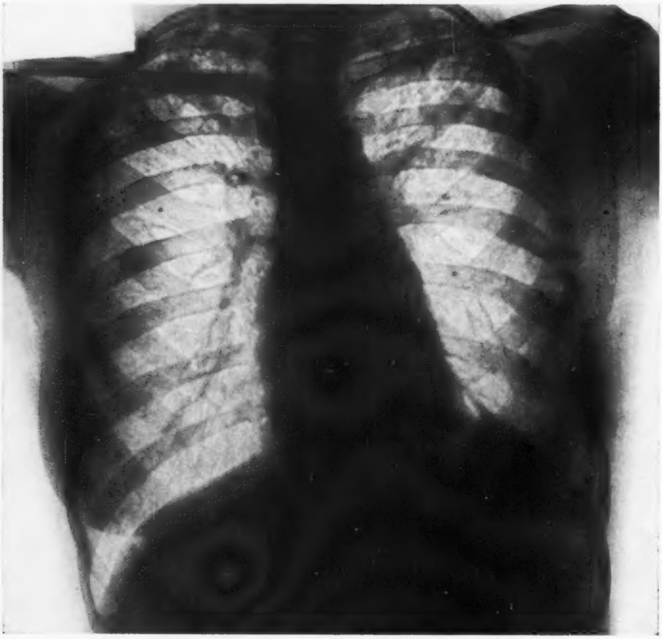

Fig. 19.—Case XII. Mediastinal effusion after absorption. Note adhesion of the left diaphragm to the pericardium.

clinical history and symptoms effectually excluded these conditions. The presumption that the shadow was due to a collection of fluid near the mediastinum was verified by the subsequent examination made two weeks later. You will now observe in this plate (Fig. 19) a dense adhesion of the left diaphragm to the pericardium. There is, moreover, a complete disappearance of

the shadow previously noted to the left of the heart. We have here, therefore, evidence of adhesions in a case of tuberculosis, by reason of which the anterior border of the lung was held in contact with the pericardium so that an effusion on its mediastinal surface was retained in this position. It is not improbable that such an effusion may be secondary to a tuberculous process on the mediastinal aspect of the lung, just as is more frequently the case in instances of intralobar pleurisy of tuberculosis later to be described.

(*b*) A collection of fluid in the mediastinal recess may in a case of empyema be a source of considerable difficulty in diagnosis. The persistence of fever and other symptoms pointing to a collection of pus in the chest after apparent evacuation of an empyema may occasionally be explained by this unusual complication. Some of the diagnostic difficulties here encountered are well illustrated by a patient who recently came under observation.

Case XIII.—This child was three months of age. For fourteen days previous to admission it had a typical pneumonia. On admission to the hospital the temperature was high and remittent, and there were signs of a large pleural effusion on the left side, which, there was every reason to believe, was a simple non-encapsulated one. At the first operation a considerable amount of thick pus was evacuated through a posterior incision. In spite of apparently good drainage, and without any evidence of retention of pus, the temperature continued and the child became increasingly septic. A physical examination undertaken at this time disclosed a slight area of dulness along the left border of the sternum in its upper part, which created a strong presumption of a pericardial effusion.

At this point I would direct your attention to the Roentgen plate taken at this time (Fig. 20), which shows what appears to be a large cardiac shadow which has every appearance of a pericardial effusion. For this reason an operation for the drainage of the pericardial sac was undertaken, and the left fifth costal cartilage was resected. The anterior margin of the left lung was adherent over the heart. The pericardial sac was

aspirated and a small amount of clear fluid containing flakes of fibrin was evacuated. The pericardium was opened and only 30 c.c. of fluid were found.

It appeared to the surgeon that the small pericardial effusion accounted neither for the persistence of the symptoms nor for the physical signs. For this reason the anterior margin of the lung was stripped away from the pericardium, disclosing at least 6 ounces of pus situated between the mediastinal surface of the

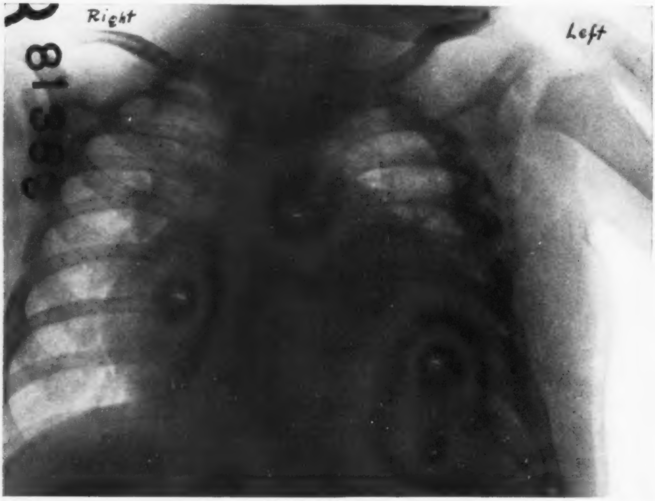

Fig. 20.—Case XIII. Mediastinal empyema simulating purulent pericarditis. The large heart shadow is due to a collection of pus between the heart and the mediastinal aspect of the left lung.

lung and the heart. In spite of drainage the patient died. It is evident that in this case a residual collection of pus was present in the mediastinal portion of the left chest which apparently was not drained by the original thoracotomy operation. I would emphasize particularly in this case the readiness with which a collection of fluid in this location was confused with a purulent pericarditis.

Encapsulated Fluid and Air.—The presence of air in the

pleural cavity in association with an encapsulated effusion introduces so many new factors of interest both in regard to the physical diagnosis and etiology that we may profitably devote a little time to its study. Although the larger collections of air in the chest signalize their presence by such characteristic signs as tympany and succussion, smaller amounts, such as are commonly found with sacculated effusions, are easily overlooked. Moreover, they may make accurate topographic diagnosis difficult or impossible by masking the underlying effusion.

Although the physical examiner finds his difficulties thus multiplied, the presence of air and fluid in the chest is a fortunate circumstance for the Roentgen examination, and it is to the latter that we owe our present exact knowledge of these cases. The principle upon which this is based is that of the hydrostatic law of fluid levels which obtains within the pleural cavity when fluid and air coexist, and there is no more distinctive sign on the plate than a sharp horizontal line of fluid surmounted by air. Not only one but several such levels may be visible in a single case, and we are enabled by varying the position of the patient to study the size and position of the sacculations.

We commonly associate the condition of pyopneumothorax with pulmonary tuberculosis, yet it is surprising to note the frequency with which encapsulated collections of air are encountered with pyogenic disease of the pleura. Aside from tuberculosis perhaps the commonest cause of sacculated pyopneumothorax is the perforation of a lung abscess into the pleural cavity or its extension to the pleural surface. Such a perforation is in the majority of the cases preceded by pleural adhesions for a long time. The resulting effusion, communicating with a bronchus, is therefore well walled off.

This complication of a lung abscess or bronchiectasis may develop during the early acute stage of the disease or, on the other hand, it may occur later and be a terminal event.

Case XIV.—Let me illustrate the sequence of events in a case of this type which recently came under observation. The patient is a man of forty-five years, who contracted pneumonia,

presumably of the influenzal type, two weeks before he came to the hospital. He had up to then a very harassing constant cough, with a moderate purulent expectoration. On the fifteenth day of his illness the sputum had a fetid odor and was blood tinged. The inference was plain that he had developed an area of gangrene in his lung. At this time the physical signs were those of a lobar pneumonia of the right lung in the stage of resolution. On the eighteenth day, without any marked aggravation of his symptoms, the area of dulness at the right base became very flat and the breathing was much diminished. Above the region of flatness a dull tympanitic note was heard, with distant caverous breathing. Succussion and metallic tinkle were easily elicited. The question now arose whether we were confronted with a rapidly forming abscess cavity or a localized pyopneumothorax due to the perforation of an abscess. The distinction between these two conditions is occasionally difficult, and it may be worth while to summarize the considerations pro and con as we weighed them at the time.

In Favor of Lung Abscess.—1. The known existence of a lung abscess with the expectoration of large amounts of fetid sputum.

2. The physical signs which would correspond to those of a large cavity.

In Favor of a Localized Pyopneumothorax.—1. The marked superficial dulness, which suggested a pleural effusion.

2. Demonstration of a shifting fluid level which was very distinct. This sign as evidence of a cavity can be elicited only in exceptional cases.

3. The improbability of the development of so large a cavity as was indicated by the physical signs in a few days.

4. The fluoroscopic examination, which indicated a collection of fluid and air on the surface of the lung, not in its depth. The plate (Fig. 21) shows the horizontal level of fluid, which is surrounded by a dense adhesion on all sides.

This patient was operated and, as predicted, a walled-off collection of foul-smelling pus was found and evacuated. A superficial perforated abscess of the lung was found. The patient rapidly improved and was discharged well some weeks later.

Such acute pyopneumothoraces have been encountered with remarkable frequency during the recent epidemics of influenza-pneumonia, in cases in which a cortical area of pneumonia underwent suppuration and even gangrene. As far as the cure of the suppurative pulmonary process is concerned, this complication appears to be, at least in some cases, a favorable occurrence, as

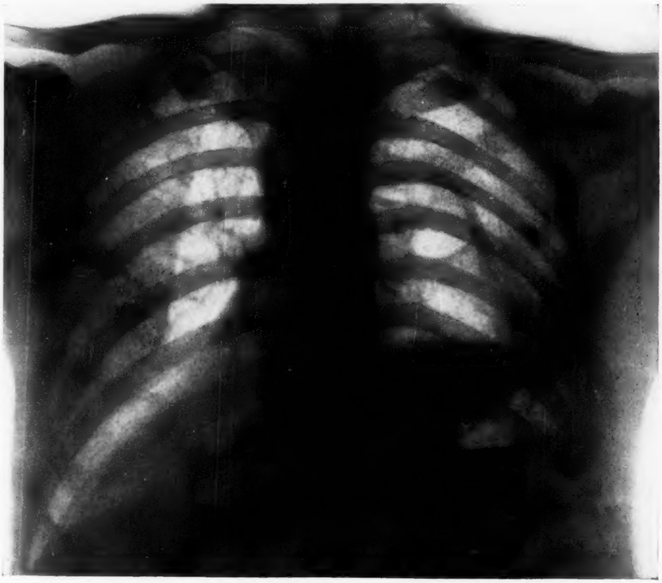

Fig. 21.—Case XIV. Encapsulated pyopneumothorax following rupture of lung abscess. Note dense adhesions about the fluid and air.

it leads to early drainage both of the lung abscess and of the empyema.

The underlying disease of the lung may in other cases be less obvious. A chronic indurative pneumonia with multiple bronchiectases may have been symptomless for some time until the rupture of a bronchiectatic abscess leads to a sudden pyopneumothorax. Especially in the case of young children must the pos-

sibility of a lung abscess due to the aspiration of a foreign body be borne in mind. In these patients the existence of a foreign body may not be suspected for a long time until either bronchoscopic or Roentgen examination reveals it, and the first evidence of serious pulmonary disease may be a localized pleural effusion.

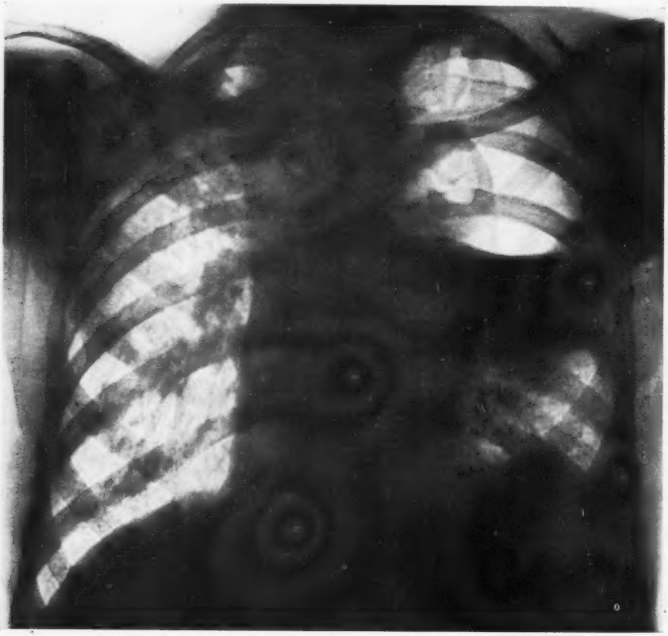

Fig. 22.—Case XV. Encapsulated pyopneumothorax, tuberculous. Note above, pneumothorax and compressed lung with cavity; below, adherent lung and the fluid suspended between.

CASE XV.—Pulmonary tuberculosis is a fruitful source of encapsulated pyopneumothorax. The pleural adhesions which are almost the rule in cases of chronic tuberculosis are very prone to wall off such effusions. A unique result of this is seen in Fig. 22. You will note in the middle of the left chest a dense shadow of fluid. The latter does not extend to the base, but is supported

by adherent lung some distance from the diaphragm. Above the fluid, which has a horizontal level, a pneumothorax extends to the apex. The collapsed upper lobe, containing a large cavity, in seen near the upper mediastinum. The physical signs were the classical ones of a pyopneumothorax, except that, instead of extending to the base, the area of flatness corresponding to the fluid ceased at the angle of the scapula, whence there was good resonance to the base.

In contradistinction to the cases we have thus far considered in which the air in the pleural cavity originated from a perforation of the lung or a bronchus are those in which the air is introduced from without, either unavoidably during operation or accidentally during aspiration of the chest. You are all familiar with the residual collections of pus which may remain in the chest after empyema operations, communicating with the external wound by a more or less tortuous sinus. The complicated conditions which here obtain can rarely be unraveled by physical examination, and the surgeon must be guided by his probe or the Roentgen examination after the injection of the cavity with bismuth. In some cases, after operation, a collection of fluid and air may occupy an unusual location, such as the mesial portion of the chest. Let me recall to you the patient with an encapsulated axillary empyema (Case I, Fig. 2), with whose history and operative findings you are already familiar. His postoperative course was a stormy one and for three or four days, in spite of a diminishing discharge from his drainage-tube, his temperature and prostration were considerable. On examining his chest for evidence of retained pus there was found an area of dulness along the right border of the sternum which extended from the second to the fifth costal cartilages. The Roentgen plate (Fig. 3) showed a collection of fluid in the mesial portion of the right chest, well encapsulated, and surmounted by air.

Now it is a matter of interest to understand how this mesial empyema arose. It was not present before operation, as both the physical examination and the plate testify. It therefore must have developed after the operation, and the mode of its origin can be apprehended by a study of the plate. You will

note the area of pneumothorax in the right axilla, which represents the site of the effusion which has been evacuated. You will also observe the thickened edge of the not yet expanded lung along the margin of the area of pneumothorax. It is probable that during the operation the surgeon, while probing the limits of the empyema, broke down some of these adhesions, carrying infection into the previously uninvolved mesial part of the pleura. In this patient, on the discovery of the location of the fluid, a needle was introduced in the second interspace close to the border of the sternum. Pus was found superficially and evacuated by incision and drainage. This patient is now quite well.

Naturally, aspiration of the chest in this unusual location should only be performed after the operator has assured himself that important structures, such as the heart and great vessels, are in their normal positions. Once assured of this by a previous fluoroscopic examination, which should always be performed, he may without hesitation insert the needle over the area of dulness corresponding to the effusion.

The introduction of air into the pleural cavity during exploratory aspiration may bring to light a sacculation of the effusion which was previously only suspected. I believe that the accidental introduction of air is more apt to occur in the case of encapsulated effusions, because the lung being bound down by adhesions, is prevented from expanding after the removal of the fluid, and air is therefore drawn in through the needle under the influence of the negative pressure in the chest.

Case XVI.—The instructive results which follow are illustrated by the case of a young woman, the important facts of whose history I will recount to you. Following pneumonia six weeks before admission a pleural effusion developed in her left chest. Two weeks later 600 c.c. of clear fluid were withdrawn. She remained well for two weeks, when she once more became ill, with fever and cough. On admission to the hospital she presented the physical signs of a fairly large accumulation of fluid in the chest. Aspiration was then attempted posteriorly in the eighth space, but without success. A second aspiration was

performed at the level of the fourth space and only 50 c.c. removed. The needle was repeatedly inserted in the neighboring interspaces, but no fluid was obtained. None the less there is no doubt that there were several sacculations, as the Roentgen plate, made the next day, showed at least three fluid levels

Fig. 23.—Case XVI. Multilocular pyopneumothorax showing three fluid levels, patient in lateral recumbent position. A case of serous encapsulated effusion, infected by multiple aspirations.

(Fig. 23). The air introduced during aspiration brings out sharply the separate fluid collections, the limits of which are better shown with the patient in the lateral recumbent position. The sequel of this case is also of interest. The pleural fluid became rapidly infected with anaërobic organisms. The tem-

perature was high and the patient septic. Physical examination two days later revealed the typical signs of an unencapsulated pyopneumothorax. Evidently, under the influence of the putrid infection, the adhesions were dissolved and the various sacculations coalesced into one large effusion surmounted by air, as is

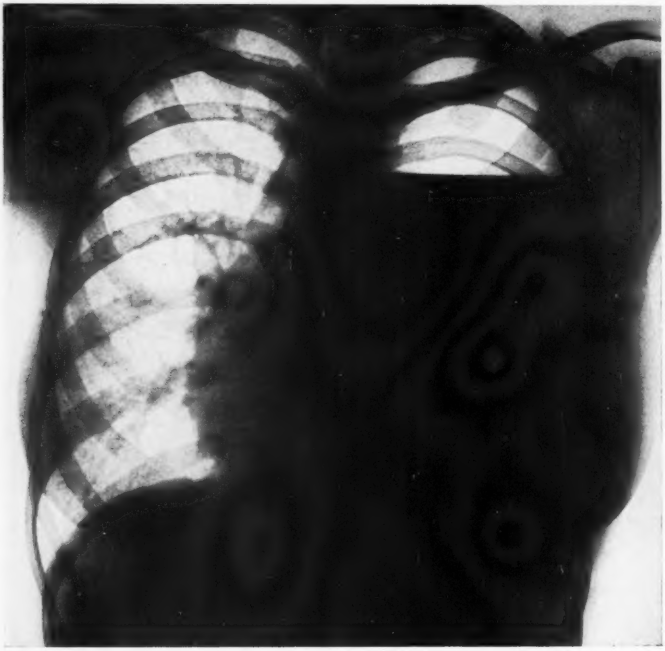

Fig. 24.—Case XVI. Multilocular pyopneumothorax, after solution of the adhesions by anaërobic infection; result, one large pyopneumothorax.

graphically shown in Fig. 24. After operation and the removal of 3 pints of foul-smelling pus the patient promptly recovered.

4. INTERLOBAR EFFUSIONS

Of all effusions in the chest, the interlobar ones offer the greatest difficulty in diagnosis, for evident reasons. Situated between

the lobes of the lungs and covered completely by them such effusions produce auditory phenomena which are often partly or completely masked by overlying pulmonary tissue. It may be stated at once that interlobar effusions are of great rarity, and the more carefully we analyze the cases in which the diagnosis is advanced, the fewer are the authentic ones. You will occasionally observe the tendency among some clinicians to speak of an effusion as interlobar if an area of dulness is found localized at the region of one of the interlobar fissures. Yet, if for no other reason than its great rarity, such an inference is a hazardous one and the greater

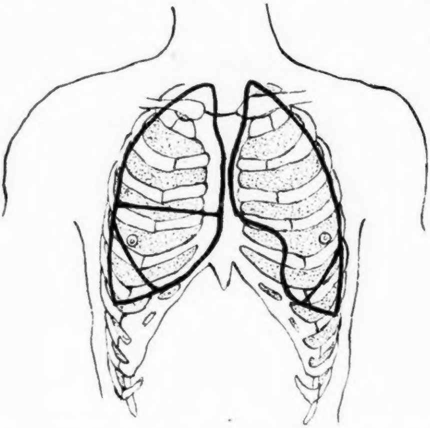

Fig. 25.—Location of the interlobar fissures. Anterior view.

probability would inhere in a diagnosis of simple encapsulated pleurisy in most of these cases.

In order to have a clear idea of the location of these effusions it is necessary to bear in mind the topographic relations of the fissures, especially of those on the right side where most of the effusions occur. This is indicated in Fig. 25. The important points to bear in mind are the course of the upper interlobar fissure on the right side, which extends transversely across the chest from the sternal end of the fourth rib to the axilla. It extends to the posterior axillary line, where it meets the lower fissure. The plane of this fissure is, therefore, horizontal. The

lower fissure begins at about the sternal end of the sixth rib, curves upward to the axilla, and then ascends sharply upward, approaching the spine at the second or the third dorsal vertebra.

By far the greater number of interlobar effusions are found on the right side and usually accumulate in the fissure between the upper and the middle lobe. Three general causes may be considered in explanation of interlobar effusions:

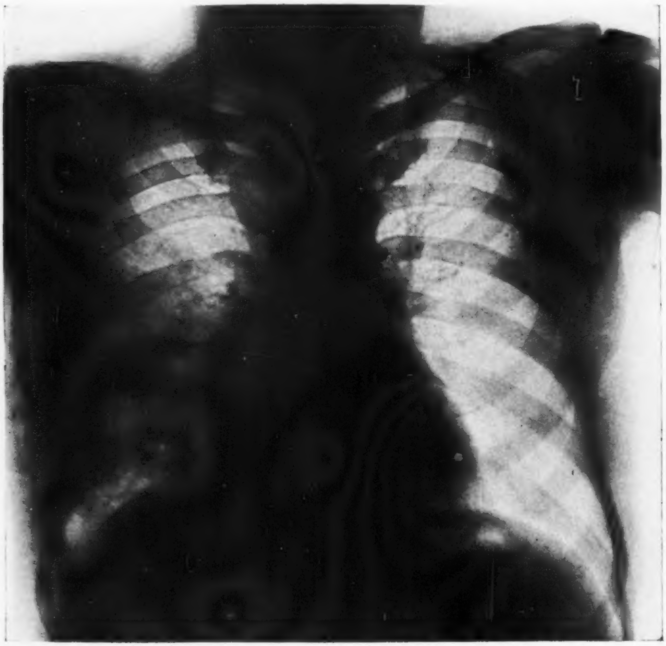

Fig. 26.—Case XVII. Interlobar effusion. Lenticular shadow in the middle of right chest, surrounded by pneumonic infiltration.

First are the metapneumonic ones, which are often serous and are ultimately absorbed, so that they remain latent throughout their course.

The second cause is pulmonary tuberculosis, which must be considered a frequent one, especially in children.

Finally, there are idiopathic cases in which there is no discoverable association with pulmonary disease and in which perhaps the effusion is the result of a primary infection of the pleura.

Case XVII.—I will attempt to illustrate these different types for you. I will first present to you a middle-aged man who has been affected for two weeks with pneumonia of his right lower lobe, with the usual physical signs. There is no evidence of a fluid accumulation in his chest. However, because of the unusual duration of his illness, a Roentgen examination of his lungs was made, which I now show you (Fig. 26). You will note at the upper limit of the pneumonic area a circumscribed dense crescentic shadow in the region of the right upper interlobar fissure, which is undoubtedly due to a small amount of fluid within it. Whether it was serous or purulent could not be determined at the time of the examination, but the rapid defervescence and the complete cure of this patient leaves no doubt that we were here dealing with metapneumonic serous effusion. Of course these small collections of fluid are not demonstrable by physical examination.

Case XVIII.—Other cases, however, have not such a fortunate outcome. Let me recite to you the history of a child one year of age who recently had a typical pneumonia of the left lower lobe. The clinical course was stormy, with very high temperature, prostration, and toxemia. Although the pneumonia after two weeks showed signs of resolution, the temperature remained high. The physical examination indicated an almost complete disappearance of the pneumonic process, and we were at a loss to explain the high fever. A Roentgen examination which was then undertaken showed on the right side a dense linear shadow in the region of the interlobar fissure, which was not present on the previous examination, when only the left lower pneumonia was found. The child succumbed to the infection, and at autopsy a small amount of pus was found in the right interlobar fissure (Fig. 27).

It is not improbable that these small interlobar effusions occur more frequently than is indicated by our clinical experience.

It must be remembered that the space between the upper and the middle lobes is a very narrow one and at most can accommodate but a small amount of fluid. It is therefore likely that when the effusion increases to a measurable extent it will burst its adhesions and infect the general pleural cavity. The resulting empyema will therefore mask the underlying interlobar effusion from which it originated. It has thus been the experience of surgeons to find occasionally in cases of empyema in the pleural

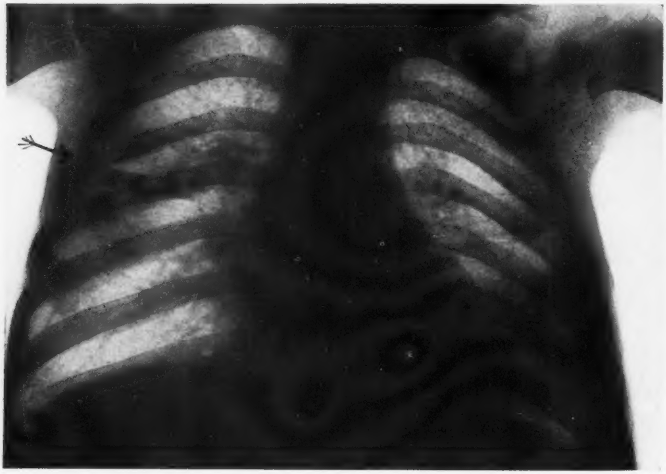

Fig. 27.—Case XVIII. Purulent effusion in right upper interlobar fissure. Resolving left lower pneumonia.

cavity a small collection of pus in addition within one or more of the fissures. On the other hand, such an interlobar effusion may seek an outlet elsewhere by rupture into the bronchus, thus evacuating itself through the mouth.

Case XIX.—I am fortunate in being able to illustrate to you graphically this extension of an interlobar effusion into the general pleural cavity, in the case of a child eight and one-half years of age who for three months has been suffering from head-

ache, fever, and weakness. Six weeks ago she developed a pain in the right side, with a dry cough and evening temperature. You will observe that this patient is pale and undernourished, and is apparently suffering from a subacute infectious disease. The examination of the chest reveals on the right side posteriorly dulness below the angle of the scapula, with an absence of fremitus

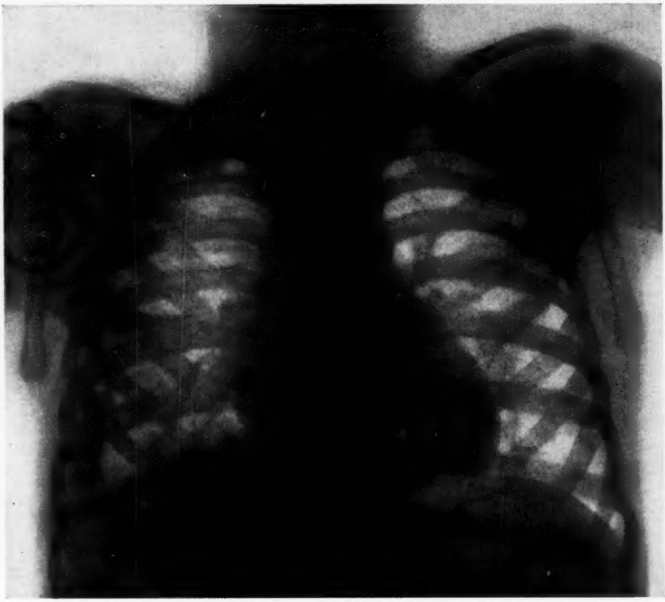

Fig. 28.—Case XIX. Empyema in right interlobar fissure with extension into the general pleural cavity. Note shadow in the axilla, continuous with that of the interlobar effusion.

and voice sounds. The physical signs indicate apparently a small pleural effusion. The white blood count is 16,000; polynuclears, 63 per cent. The temperature is not higher than 100° F. Aspiration produced a small amount of clear fluid in which there were a moderate number of lymphocytes. Although there was nothing in the physical examination to suggest the presence of an interlobar effusion, the Roentgen plate which I show you

(Fig. 28) discloses the typical shadow of a small effusion in the upper fissure and also its extension outward into the general pleural cavity, which it partly fills. In this case the condition—at least from the history and the cytology of the pleural fluid—strongly suggests a tuberculous pleurisy.

Case XX.—On the other hand, the general pleural cavity and the interlobar fissure may be simultaneously infected. A child of sixteen months contracted measles about one month

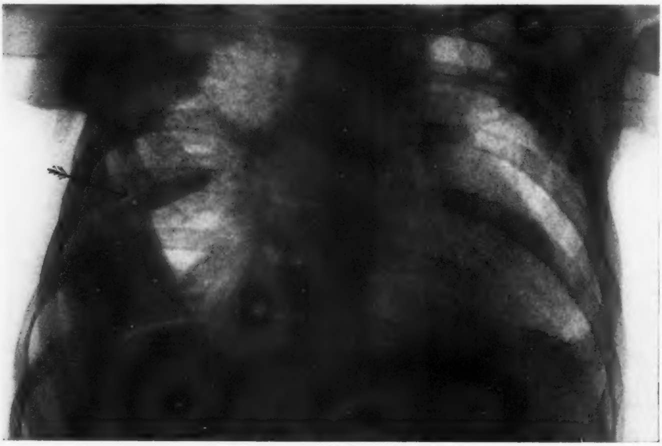

Fig. 29.—Case XX. Interlobar empyema and encapsulated axillary empyema in the same patient. Arrow points to small amount of pus in the fissure between the upper and the middle lobes.

ago. For two weeks she had continued slight temperature and cough. On admission to the hospital she had dyspnea, was emaciated, and had pain in the right chest on respiration. On examining the chest there was found flatness on the right side from the spine of the scapula not quite to the base in the axillary half of the chest. There were a few râles in the midaxilla. Operation in the eighth space, posterior axillary line, disclosed an encapsulated effusion containing 12 ounces of pus. In addition, on separating the upper and middle lobes a small amount of pus

was found in the fissure. The conditions are graphically portrayed in the plate (Fig. 29) which was made shortly before the operation. There is an irregular shadow in the apical and axillary regions, corresponding to the encapsulated effusion. Of particular interest, however, is the crescentic shadow in the middle of the right chest, due to the small interlobar effusion. It is needless to state that the physical examination cannot hope to disclose such a small effusion, and we are here entirely dependent on the Roentgen examination, which has been of the greatest service in these cases.

In contradistinction to the cases of metapneumonic interlobar effusion are those which develop without any evident pulmonary disease. The etiology of these cases is as abscure as their physical signs, and in the absence of a Roentgen examination they are in all probability usually regarded as deep-seated pneumonias or as acute respiratory infections of unknown type.

CASE XXI.—This form is well illustrated by a child ten years of age who has had all the symptoms of an acute respiratory infection for ten days. On physical examination there were originally noted the usual dyspnea and cough. Physically, only on the most careful percussion was a slight area of dulness elicited anteriorly at the level of the second and third intercostal spaces. There were no breathing changes or râles. The Roentgen plate taken at the height of the fever (Fig. 30) showed a small interlobar effusion, the shadow of which was typical in both shape and location. After a few days the temperature came to normal and the child convalesced. A subsequent plate showed the complete disappearance of the shadow. We were evidently dealing here with an acute pleurisy with effusion in an unusual location which, as may be judged from the outcome, was serous rather than purulent. In this case the acute inflammatory nature of the process was further attested by the high blood count, which was 22,000; polynuclears, 80 per cent.

Small effusions within the right upper fissure are occasionally aspirated for purposes of diagnosis, with varying success. When

it is borne in mind that probably in most cases there are but a few cubic centimeters of fluid within the fissure, it is not surprising that it will often escape the aspirating needle. It is usually necessary to insert the needle deep into the lung, especially if the aspiration is made from the axilla. In some cases greater success is achieved if the exploration is made anteriorly in the mammary line.

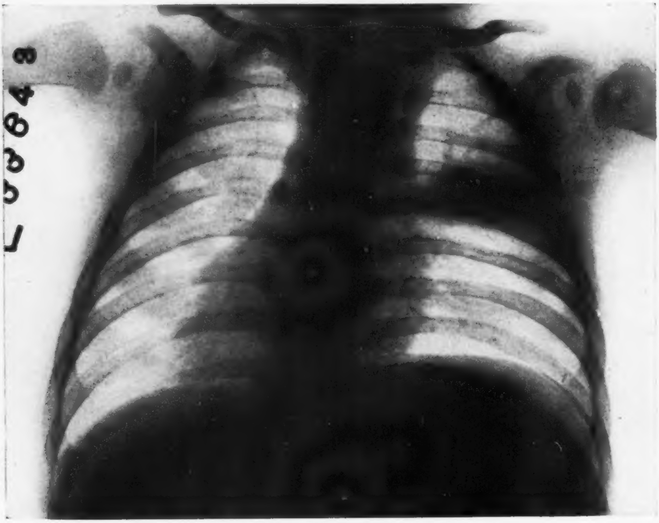

Fig. 30.—Case XXI. Primary, non-suppurative effusion in the upper interlobar fissure.

Little can be said in regard to the physical signs of interlobar effusions. They are rarely characteristic, and in many cases—especially in small effusions—they are entirely wanting. In the larger effusions there is usually dulness at the site of the fluid with a tympanitic note above it which is produced by the compressed upper lobe; although when marked dulness and other physical signs are present the effusion has already exceeded the bounds of the fissure and has invaded the general pleural cavity.

Occasionally we discover an interlobar effusion accidentally

during the course of a routine examination of the chest, and we may then be at a loss to explain its occurrence.

CASE XXII.—Observe this patient, thirty-five years of age, who for some months has suffered with the usual symptoms of hyperthyroidism. He has at present no symptoms of any kind,

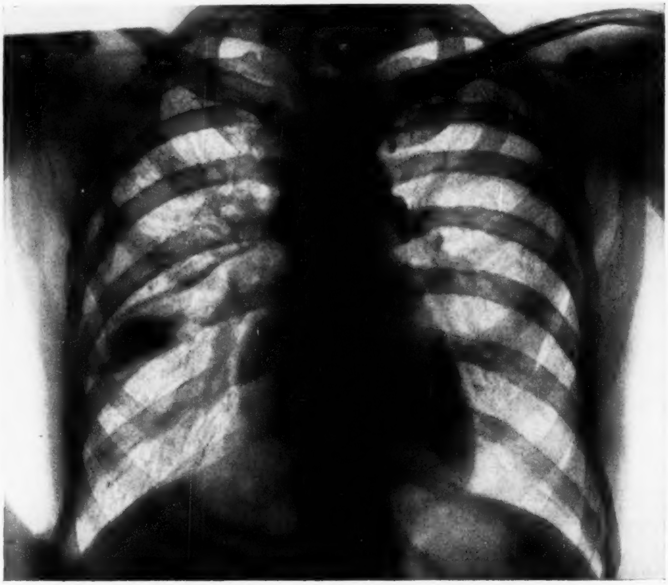

Fig. 31.—Case XXII. Interlobar effusion, latent, probably postinfluenzal. Note the linear shadow indicating the posterior margin of the fissure.

but relates that before his admission to the hospital he had an attack of influenza. His respiratory organs reveal no abnormality. In order to determine the size of his heart a Roentgen examination was made, and to our surprise we discovered a typical interlobar effusion on the right side (Fig. 31). How is this to be explained? Has he had an unrecognized influenzal pneumonia with associated interlobar effusion, or did he have the latter

alone? No one can say. A later Roentgen examination has shown that this effusion has already completely disappeared.

In cases of interlobar pleurisy, especially in children, it is always proper to consider the possibility of an underlying tuberculous affection of the lung. The studies of Ghon in regard to primary tuberculosis in children have revealed the frequency of early lesions in the right upper lobe near the pleural surface and that they are often accompanied by changes in the pleura of either a plastic or a serous character. These serous effusions in the fissures may be transient or of some duration, and their absorption leaves in their wake a thickening of the pleura in this region which may be evident years after on the Roentgen plate as a linear shadow across the right upper chest. It is probably safe to consider many of the transient interlobar effusions as metapneumonic, and those which persist as tuberculous.

Let us in conclusion devote a few moments to a consideration of effusions between the upper and the lower lobes and those between the middle and the lower lobes. I present this part of our subject with hesitation because the clinical picture of these cases is not clear cut and the diagnosis of effusion in these uncommon locations is never a secure one. These effusions are even more uncommon than those in the upper fissure.

Case XXIII.—The patient I now present to you is twenty-one months old. He had pneumonia four months ago, since which time he has had a constant cough. There have developed recently enlarged, probably tuberculous, cervical lymph-nodes. For four days previous to admission to the hospital he had a slight temperature, especially in the evening. On admission he was only slightly ill. Examination of the chest revealed dulness posteriorly from the apex to the angle of the scapula; below this, and extending into the axilla, there was a tympanitic note. Anteriorly the percussion note was in general tympanitic. The breathing sounds posteriorly in the upper portion of the chest were bronchial in character and below were bronchovesicular. The von Pirquet reaction was strongly positive. A needle was inserted posteriorly in the usual location and only a few drops of

clear fluid were obtained. When the needle was inserted deeply in the axilla, however, a considerable amount of clear gelatinous fluid was aspirated. This fluid was sterile on culture. We have here, therefore, a collection of fluid which is presumably encapsulated, situated toward the posterior aspect of the chest and leaving the extreme base uninvolved. The previous history of

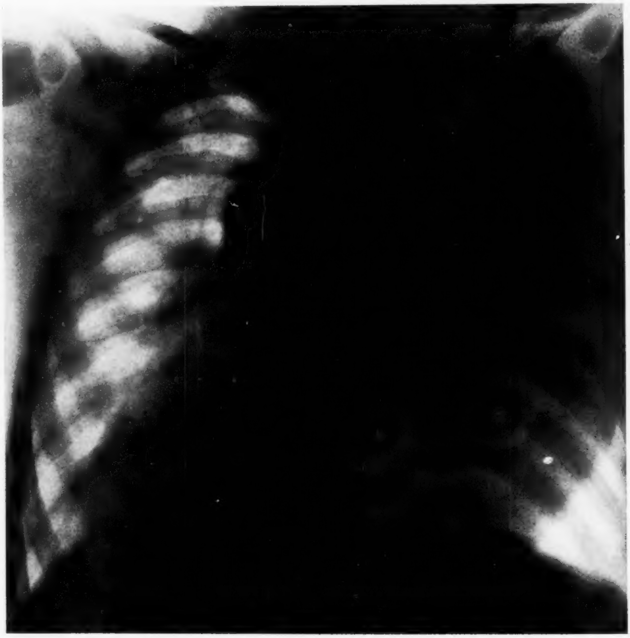

Fig. 32.—Case XXIII. Large serous effusion in the fissure between the right upper and lower lobes.

respiratory disease, together with the development of tuberculous lymph-nodes and the positive von Pirquet test, which at this age has some significance, creates a strong presumption of a tuberculous pleurisy. From the physical signs alone it would be hazardous to venture an opinion as to the exact location of the fluid, whether it is in the fissure between the upper and lower

lobes or on the posterior aspect of the chest. I would call your attention to the Roentgen plate (Fig. 32) in this case, as it may be regarded as typical of a large effusion between the upper and lower lobes. You will note that the axillary portion of the chest below is uninvolved and that the heart is displaced toward the left side. This child left the hospital apparently well, the effusion producing no marked symptoms.

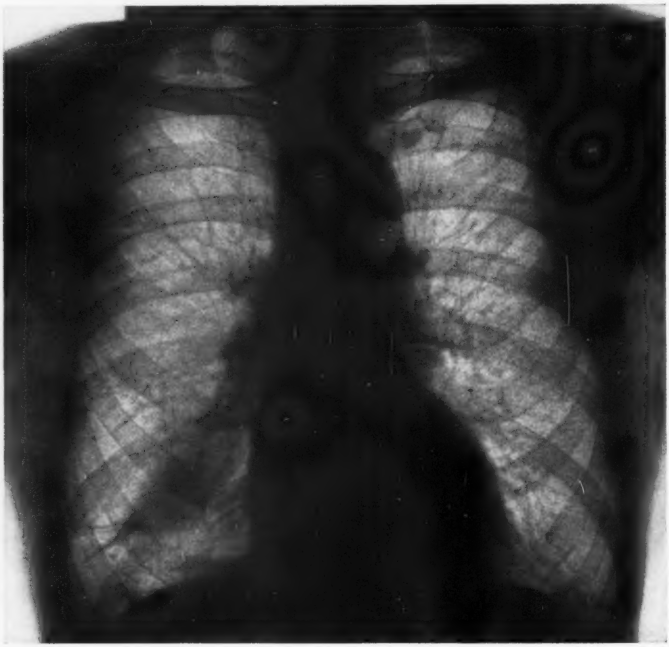

Fig. 33.—Case XXIV. Small effusion in the right lower fissure. Edge of the fissure thickened.

CASE XXIV.—Whereas such large interlobar effusions may give rise to physical signs, it is readily understandable that smaller ones, when they are completely surrounded by lung tissue, may be entirely latent, both symptomatically and as to physical signs. For example, in Fig. 33, a small effusion is seen in the right lower

fissure near its anterior extremity, the existence of which was unsuspected and which was discovered incidentally during a fluoroscopic examination of the patient's heart. The thickened edge of the fissure is also visible as it extends from the region of the effusion to the lateral chest wall.

THE SECONDARY CHANGES IN THE CHEST ASSOCIATED WITH ENCAPSULATED EFFUSIONS

It must be apparent to you that the diagnosis of localized effusions in the chest will often be attended by real difficulties. Clinicians have always been conscious of the limitations of the physical examination and usually have made the diagnosis with a measure of hesitancy which is quite warranted. They have, therefore, sought for any physical changes in the chest which might have some significance in distinguishing these cases from free effusions. It may be worth while to discuss some of these changes and to appraise their value.

A retraction of the ribs over a pleural effusion has been regarded by some clinicians as evidence of its encapsulation. In support of this view it may be stated that frequently such a drawing together of the ribs does occur, and in the more chronic cases with the formation of dense adhesions and the accompanying atelectasis of the lung it may become extreme. The value of the sign, however, suffers consideraly from the fact that it may also occur with unencapsulated effusions.

This sign can perhaps be better gaged by a study of the conformation of the chest on the Roentgen plate rather than by inspection or mensuration. It is, therefore, instructive to note that in a large percentage of cases of acute inflammatory pleural effusion the ribs are drawn together. This phenomenon finds its explanation in the reflex contraction of the intercostal muscles in inflammatory conditions of the underlying viscera. For a similar reason it is present in acute tuberculosis and it is analogous to the reflex rigidity of the abdominal wall due to peritoneal irritation. A marked separation of the ribs is usually found only in large non-inflammatory effusions and occasionally in cases of empyema in children in which the effusion has been a very rapid

one. It is evident, therefore, that a retraction of the ribs cannot be regarded as a reliable sign of encapsulation of an effusion. On the other hand, even with encapsulated effusions, when they are under great tension, there may be an actual separation of the ribs. This is illustrated in Case IX (Fig. 13), in which after the evacuation of two collections of fluid in the lower portion of the chest a residual collection was found under great tension in the upper left region. The marked separation of the upper ribs is distinctly visible in the plate.

Another sign which is supposed to bear indirectly on the diagnosis of encapsulated as opposed to free effusions, is an absence of a displacement of the heart. In order to appraise the value of this sign it is necessary to bear in mind the physical conditions that determine the position of the heart within the chest. It maintains its position as a result of the elastic tension exerted by the lung on each side of it through the medium of the negative pressure within the pleural cavity. Any factor which upsets the balance of tension will tend to a movement of the heart from its normal position. The relaxation of the lung which results from an inflammatory process on its pleural surface will diminish the elastic pull of the lung on the mediastinum and the heart so that they are drawn over by the unopposed traction of the opposite lung. In the case of large effusions there is probably added the element of increased intrapleural pressure on the involved side, which also tends to push the heart to the opposite side.

If we keep these considerations in mind, it will be clear that in respect of their effect on the position of the heart there should be no difference between free effusions or encapsulated ones of moderate size. This is, in fact, borne out by experience. Roentgen examination shows that the heart is displaced little if at all by free effusions of moderate size and the same is true of most sacculated effusions. On the other hand, even a small encapsulated pleurisy may cause a displacement of the heart if it is so situated with respect to its borders that it can exert direct pressure on them. This is well illustrated in the patient I have already presented to you in whom there was a basal encapsulated effusion (Case V). You will note in the plate taken before opera-

tion (Fig. 7) that the fluid, which was closely applied to the left border of the heart, pressed directly upon the latter, so that it, together with the mediastinum, was dislocated to the right. It is instructive to note the return of the heart to its normal position after the removal of the pus (Fig. 8).

Similarly, if you will recall the cases of mediastinal effusion which I have already presented to you, you will note (Figs. 18, 19) that the fluid which was closely confined by adhesions along its left border is in a most favorable position to exert pressure on the heart and therefore to displace it. Here again, after the absorption of the exudate, the heart returned to its usual position.

I should like, therefore, to leave with you this thought in connection with the diagnosis: In estimating the probability of an effusion being encapsulated, it is wise not to focus the attention too closely on any one or more physical signs which in occasional cases may have special applicability. It is wiser to weigh all the symptoms and signs in the balance and also to take into account all those factors in the etiology of the case which would favor encapsulation.

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THE TREATMENT OF ADVANCED HEART FAILURE [1]

Few conditions which are so gravely threatening to life as advanced heart failure offer equal opportunities for the successful exercise of therapeutic skill, and at the same time there are few which make greater demands upon the skill of the therapeutist. While all treatment is foredoomed to fail in some cases, in many others we are rewarded with the rare satisfaction of being able to restore a well-nigh helpless invalid to a life of comparative comfort and more or less usefulness, which may be prolonged for periods measured in years. Even in the cases in which we are faced with disappointment from the beginning we can still frequently do much to alleviate the suffering and anguish which so often characterizes these cases. Success in treatment demands minute attention to detail and strict individualization, hence no routine plan can be laid down, except to serve as a general outline of procedure to be modified and amplified to meet the particular conditions arising in each patient. The present discussion is intended to serve as a guiding outline, more or less amplified, but still subject to such further modifications as the circumstances may dictate.

It is not our purpose to enter into the etiology, symptomatology, and diagnosis of advanced heart failure except in so far as they influence treatment, nor shall we deal with those cases arising in the course of acute infections. We shall limit our discussion to that large group of cases of advanced heart failure

[1] This represents a combination of material from the author's own cases and from the more recent literature. Case records have been omitted.

which occur as the result of chronic cardiac or cardiovascular disease. The primary causes of the heart disease are usually of remote occurrence in these cases, and have generally ceased to exist except in those cases due to syphilis or to progressive vascular disease. The damage to the heart has already been done and the primary organic changes, upon which the failure rests, are generally of long standing and more or less stationary. Treatment is powerless to alter the structural changes which have taken place, though it may be possible in the syphilitic and vascular cases to check the further progress of the underlying disease more or less effectively, or at least to delay the advancing changes. While the primary cause or causes of the heart disease are not amenable to treatment in the stage with which we are dealing, they should nevertheless be sought out and analyzed, since they not infrequently modify the course of treatment and always influence the prognosis.

There is another group of etiologic factors, however, consideration of which is of the utmost importance in the treatment of advanced heart failure, namely, those factors which are directly or indirectly responsible for precipitating the attack of failure. Unlike the first group, these factors are almost invariably subject to control or removal, and adequate attention to them is one of the most important elements in the management of these cases, both with reference to the relief of the existing failure and as a means of preventing the subsequent recurrence of failure.

Advanced failure may be divided into several more or less definite types for the purpose of simplifying discussion, since the response to treatment differs with the type. That type which yields most dramatically to treatment comprises most cases of auricular fibrillation of rheumatic origin and some cases developing as the result of senile cardiovascular changes. Of the non-fibrillating cases, the type due to rheumatic myocarditis responds best to treatment, while those due to senile myocardial degeneration and to syphilitic infection respond less satisfactorily. Finally, there are the non-fibrillating cases in which the myocardium is not the seat of extensive disease, but in which its reserve has been progressively exhausted in the endeavor to

maintain an efficient circulation in the face of mechanical disadvantages, such as extensive valvular lesions, especially mitral involvement and aortic insufficiency. In this latter group most of the advanced cases will be found among those who have had previous attacks of heart failure, recurring at increasingly shorter intervals of time and in response to ever-dimnishing demands upon the heart. The results of treatment of cases in this group may be quite favorable if the exhaustion of the heart is not too extensive, but frequently the results are not very satisfactory and recurrences occur in spite of the utmost precautions.

There are certain characteristic symptoms which occur so frequently and in such marked form in advanced failure that they are almost pathognomonic. They occur largely without reference to the type of failure or to its cause, but are the necessary consequences of the failure of the heart. They include cyanosis, dyspnea, orthopnea, and cough; edema, pleural effusion, ascites, general anasarca, and oliguria; symptoms due to circulatory stasis and congestion in various organs, especially those in the splanchnic area, such as digestive disturbances, nausea, vomiting, epigastric and right hypochondriac tenderness, and enlarged, tender liver; and cardiac or precordial pain and distress, with referred pain down one or both arms. They will be discussed more in detail in reference to their response to treatment, as well as to the appropriate therapeutic measures, but suffice it to say here that they vary widely in their occurrence, intensity, and combination in different cases, though one or more is almost invariably well marked, especially those referable to the respiratory system.

It is not possible in practice to separate sharply the various therapeutic measures which must be employed, but for the sake of clarity in presentation some classification is desirable. It is most convenient to consider the subject under the main divisions of: 1. General management. 2. Use of drugs acting upon the heart. 3. Symptomatic treatment. 4. After-treatment and prophylaxis. Every case of advanced heart failure should be investigated in the utmost detail as soon as conditions will per-

mit, but in many cases the gravity of the condition often demands the resort to immediate symptomatic and other treatment, and necessitates the postponement of the detailed examination and the close scrutiny of the past history upon which the equally important but less urgent therapeutic measures must be based. Lifesaving measures of treatment may be successfully instituted on the basis of a very cursory examination of the patient, and such an examination is often all that is justifiable in the beginning, but it is impossible to conduct the remaining treatment to the best advantage of the patient without the fullest knowledge of the many factors involved in the production of the heart failure. We have placed especial emphasis upon this point, for it is a fact that there is a strong tendency for physicians to feel that their main duty has been performed when they have tided a patient over the period in which life was imminently threatened. Satisfactory as such an accomplishment is, it is even more of a satisfaction to be able to restore the patient to a reasonably comfortable and useful life and maintain the restoration by proper care and guidance. The latter must always be the goal which we should seek in every patient, and it can only be reached by painstaking efforts on the part of the physician.

GENERAL MANAGEMENT

Rest.—The value of rest, both physical and mental, cannot be too strongly emphasized, since it is the most effective measure we have for relieving the work of the heart. The patient will usually have taken to his bed when he is first seen, but if not, he should be ordered to bed at once and kept there until cardiac efficiency has been restored. While it is generally far more satisfactory to confine the patient to bed, patients with very severe orthopnea may be rested more by being allowed to sit in a comfortable chair for at least part of the time. Sometimes they will even sleep more comfortably and restfully in a chair than in bed. It is generally the best policy to permit the patient to assume whatever position he prefers rather than to attempt to follow any fixed rule. When in bed he should be provided with a comfortable, adjustable back-rest so that he can assume any

position from the recumbent to the sitting without having to support himself by muscular effort. The accessory muscles of respiration are commonly called into active participation during the dyspnea and orthopnea, and it is often very helpful and restful to the patient to provide him with a table across his bed to lean forward upon, or to give him a similar support if he be sitting in a chair. Every attention should be paid to the small points of giving him the maximum personal comfort by providing him with the little accessories of this type, for obviously the more effective the rest, the greater is the relief to his heart.

As the orthopnea and dyspnea diminish he should be encouraged to assume a semirecumbent position as much as possible and the back-rest should be lowered slowly during the early part of convalescence until the patient can finally lie flat in bed without respiratory discomfort. When the response to treatment is favorable and prompt this is often possible during the first or second week, but in less favorable cases the semisitting posture may have to be maintained for many weeks. The tendency is to err on the side of lowering the head too early, and no harm is done by prolonging conservative treatment for longer than may be strictly necessary.

Mental rest is no less important than is physical, and this should be encouraged in various ways, depending upon the individual patient. The attitude of the physician and of those attendant upon the patient should be one of confidence in his recovery and of well-tempered cheerfulness. All petty annoyances and irritations should be kept from the patient, and he should be encouraged to keep his thoughts away from business as much as possible. Possible sources of worry should be brought to light and efforts made to eradicate them, or to get the patient to forget them for the time. Much worry or anxiety will largely undo the beneficial effects of all therapeutic measures, hence they must not be permitted. We are convinced that far too little attention is devoted to the elimination of such malign factors as these, because their presence is not obvious and is often discoverable only by close interrogation of the patient.

During the acute stage the patient should not be permitted

to do anything for himself, even so slight as reaching for a drink or arranging his bedclothes. Visitors should be excluded almost entirely, and the patient should be disturbed as infrequently as possible. In short, everything should be looked after which is directly or indirectly conducive to mental and physical rest, and attention to detail is the keynote of successful management to secure these ends.

Sleep, if anything, is even more important than rest, and those factors which are conducive to rest and comfort are also conducive to sleep. They, however, are seldom sufficient, and in the acute stage at least sedatives and hypnotics are generally needed. The milder sedatives and hypnotics are frequently insufficient, but whenever it seems possible that they will suffice they should be given the preference over morphin or other of the more powerful agents. In some cases of advanced failure the subjective symptoms are relatively slight and do not distress the patient greatly. Sleeplessness in such patients may be controlled more or less effectively by the administration of the bromids. From 1 to 2 grams (gr. xv–xxx) of sodium potassium or ammonium bromid should be prescribed to be taken three times daily. The bromids should invariably be given well diluted with water or milk (half a glass), and preferably immediately after the taking of some food. When their taste annoys the patient it can be effectively masked by the use of a charged water for dilution in place of plain water, but many of these patients cannot take charged water comfortably. If the bromids are well diluted there is no tendency for them to irritate the stomach. Watch must always be kept, when using large doses, to detect the earliest evidences of bromism in the form of the characteristic skin eruptions. It has been a common belief that ammonium bromid is to be preferred to the sodium or potassium salt, especially in cases of the type under discussion, as it is held to be less depressing to the heart. There is no satisfactory evidence to support this belief. Potassium bromid has been said to have a depressant action on the heart through its potassium radical, but in the doses ordinarily given there is no reason to believe that such an action can take place. It makes no difference,

therefore, which of the salts is selected, but since sodium bromid is the cheapest and most generally available, it will be the one most frequently chosen.

The bromids alone will commonly fail to produce the desired quota of sleep and must be supplemented by other hypnotics in most cases, but they are none the less of value in many cases by allaying excessive nervousness and anxiety, and secondarily by reducing the amounts of the more powerful hypnotics which will be required. Despite the very common belief to the contrary hydrated chloral is probably the most effective and safest of the simple hypnotics. The fact that narcotic doses of chloral directly depress the heart and cause a pronounced fall in the arterial blood-pressure in animals through that action and through vasomotor depression has led to the belief that hydrated chloral is dangerous as a hypnotic in man, especially in cases with cardiac disease. This idea has also been fostered by the manufacturers of substitutes for chloral. It is erroneous and is based upon uncritical acceptance of the facts. The doses required to narcotize normal animals are far greater proportionately than those which are required for hypnotic effects in man, and careful observations upon man have shown that effective hypnotic action is secured from doses which have no demonstrable influence on the heart or the blood-pressure other than that which is the direct result of increased quietude and sleep. The dose of hydrated chloral should be just sufficient to produce the desired effects and it may be prescribed in either of two ways: A dose of 0.3 gram (gr. v) may be given every four hours until the patient becomes somewhat drowsy; or twice as much may be given about an hour before the time for sleep in the evening, or twice daily, morning and evening. Hydrated chloral is eliminated rather slowly, so that when drowsiness develops the dose and the frequency of its repetition should be diminished. Like the bromids, it is capable of irritating the stomach and should always be given in dilute solution to avoid this side action. It may also be administered by rectum. It is more effective when combined with the bromids than when given alone and the dose required is usually smaller.

Barbital (veronal) or barbital-sodium (medinal) may be prescribed as substitutes for hydrated chloral, but in smaller doses. They do not possess any advantages over chloral and are not less toxic in amounts required to produce an equal degree of hypnosis. Sulphonethylmethane (trional) and sulphonemethane (sulphonal) may be tried, but the former is seldom adequate as a hypnotic in these cases, and the action of the latter is so slow in developing and so persistent that its effects cannot well be controlled. Were it not for its disagreeable properties paraldehyd would be the ideal simple hypnotic for use in the cases under discussion, for it is devoid of depressant effects on the heart and circulation except in truly enormous doses. Its taste is very unpleasant and is not easily masked, it is irritant to the stomach, and it imparts a very disagreeble and persistent odor to the breath. When it is to be given the pleasantest way is to dilute it with aromatic elixir in the proportion of 3 parts to 1 of paraldehyd, or it may be given on cracked ice or dissolved in ice-water. The usual hypnotic dose is 2 c.c. (♏xxx) repeated every hour or two until sleep is induced.

The majority of cases of advanced heart failure require more effective means of producing sleep than the use of the sedatives and hypnotics just reviewed, and for this purpose morphin is the most satisfactory. It is to be preferred to opium because it can be administered subcutaneously; its action develops more promptly; there are fewer side actions; and its dose can be controlled with greater precision. The hypodermic preparations representing the total combined alkaloids of opium do not have any advantages over morphin and are not to be preferred. Morphin is of special value in advanced heart failure because it produces euphoria and sleep; because it most effectively controls pain; and because it is apparently the only drug which is capable of producing sleep in the presence of the severe dyspnea and orthopnea so frequently encountered. The indications for the use of morphin are roughly: (1) The presence of marked orthopnea and dyspnea; (2) the presence of severe pain; (3) the failure to secure adequate sleep by the milder measures. The first two demand the immediate administration of morphin,

and no time should be lost in the trial of other drugs. In such cases the inital dose should be fairly large—from 10 to 20 mgm. (gr. $\frac{1}{6}$–$\frac{1}{3}$), and small additional doses should be given if required. Although there are often edema and oliguria due to renal congestion in these cases, there seems to be little danger from the use of fairly large amounts of morphin, and the beneficial results are often quite marked. If the patient responds favorably to the efforts to relieve the failure of the heart morphin will usually not be required after the first day or two, and it may be replaced by one of the other drugs discussed. Where the response of the heart is not favorable the intermittent use of morphin may have to be continued indefinitely, but every effort should be made to avoid its continuation for longer than absolutely necessary. While large doses are required in many of the very severe cases, smaller doses will commonly suffice in the majority of cases, especially if other hypnotics are also being administered, or if orthopnea, dyspnea, or pain are not intense. There is a temptation to employ codein instead of morphin, but experience shows it to be quite inadequate in the cases under discussion, and where an opiate is required morphin should be used from the first. Codein is, however, of some value as an adjunct to the milder hypnotics, especially where there is pain of moderate severity.

Diet.—The diet should be prescribed and controlled with as much care as is devoted to any other phase in treatment, yet its consideration is frequently neglected. The diet should be suited to the particular conditions present and should be altered to meet the changing conditions. One of the principal requirements to be met in the treatment of advanced heart failure being to relieve the heart of all unnecessary work, the diet, whatever may be its specific type, should be one which makes the least demands upon the heart. It should, therefore, be simple, readily digestible, not too abundant, and of relatively low protein content. The protein is of importance because protein stimulates metabolism and thereby directly increases the work of the heart. Diets for special purposes, therefore, should be constructed with these basic principles in mind.

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usually nauseated and has a distaste for food. Milk, koumyss, buttermilk, junket, custard, and the like may be permitted, but the patient should not be urged to take any food during the first twenty-four hours or so if he prefers not, and it is sometimes wise to starve the patient for the first day to prevent the aggravation of nausea and emesis which often follows the ingestion of even the simplest food. After the brief starvation, or from the beginning if food is allowed, the patient should be encouraged to take very small amounts frequently rather than moderate amounts at longer intervals, and unless the conditions prevent he should be given the food he prefers rather than one which is arbitrarily prescribed. Where there are no nausea and vomiting, or after these have disappeared, the diet should be determined by the conditions present and the objects which its control may aid in accomplishing.

Just so soon as the patient begins to enter upon his convalescence, and after the major symptoms of heart failure have disappeared, the diet should be increased rapidly by the addition of readily digestible, nutritious solid foods until a simple but adequate diet is being taken. If the Karell or "salt-free" diet has been prescribed, it should be discontinued and a more general diet should be resumed rapidly. The diet should be controlled as much by the patient's capacity to digest and assimilate his food without alimentary disturbance as by his actual needs in calories. It is far better to underfeed him for a time than to cause him distress through indigestion and gaseous distention of his stomach or intestines. When splanchnic congestion has been relieved it will usually be found that the patient can take a reasonably liberal diet without difficulty, and he should be encouraged to do so. A solid diet, providing foods which require mastication, is to be adopted as soon as the conditions will permit, as cardiac patients do not seem to tolerate kindly the liquid and semisolid diets for very long without their growing positively distasteful. In general, meat soups, sweets, and all forms of condiments should be interdicted, and the coarser vegetables should be introduced cautiously. Almost any form of digestible raw or stewed fruit may be allowed from the beginning, and these are specially

desirable, as they tend to aid in the regulation of the bowels. While the diet should be balanced, the protein should generally be kept at the lowest point at which it is sufficient to meet the bodily needs.

It would take us too far afield to enter into a discussion of the various minor, but more or less annoying, digestive disturbances which frequently complicate convalescence in cases with advanced heart disease. Aside from minute attention to regulation of the diet benefit may often be secured by one of the following measures: The administration of dilute HCl, which is best given in about 0.2 per cent. solution, one-half to one glass of which should be sipped with each meal, often aids gastric digestion and relieves gastric flatulence. Tincture of nux vomica and the simple bitters, or the aromatics, are often also helpful. For intestinal flatulence the administration of buttermilk, koumyss, fermented milk, or of cultures of the Bulgarian bacillus or of the Bacillus acidophilus are frequently helpful in addition to dietetic regulation. The so-called intestinal antiseptics are usually of little or no value. Experimentation in each individual case is usually the only method of controlling the disturbances, but it should always be borne in mind that some deficiency of the circulation is generally the basis for most of the digestive disorders, and that their complete control may be impossible if the circulation cannot be fully restored.

Elimination.—We will here deal only with the subject of elimination as a part of general management, leaving for later consideration such eliminative procedures as diuresis and purgation, which belong properly among the more specific therapeutic measures. This leaves only the question of the general management of the bowels, which may be dismissed in a few lines. The usual care should be taken to see that the patient's bowels are evacuated daily, but special attention should be given to the matter of preventing the patient's straining at stool. In general, only the milder cathartics and laxatives should be used unless there is some special indication for more drastic measures, and preference should be given to those which act chiefly upon the large intestine, such as cascara, aloes, and others of the anthracene

group. These cathartics in just sufficient doses produce a minimum of irritation and lead to an evacuation which is easy and which does not require much effort on the patient's part. The dose may be adjusted to the needs and susceptibility of each individual.

Almost any one of the simple cathartic salts may be prescribed in place of the anthracenes, small repeated doses being given three or four times daily. Of the many available cathartic salts, the least objectionable for the patient to take are probably sodium phosphate and magnesium oxid. Not infrequently, since the patients are confined to bed, all of these laxatives prove inadequate, and in such cases it will often be found quite sufficient to supplement them with a glycerin suppository to start the peristalsis in the lower part of the large intestine. If this does not suffice, resort should be had to small soapsuds enemas given daily or on alternate days.

When there is much flatulence, which is not relieved by the regulation of the diet, any of the simple carminatives may be tried alone or along with the laxatives, or turpentine stupes may be used. The insertion of a rectal tube during and for a time following stuping is often very helpful. Finally, enemas containing turpentine, tincture of asafetida, or other mild irritant may be needed to bring away the gas and relieve the abdominal distention, which may be very embarrassing to both heart and respiration.

USE OF DRUGS ACTING UPON THE HEART

For direct influence upon the heart and circulation the members of the digitalis group are alone of importance, caffein, strychnin, and the like being of no real value in advanced heart failure. Within the digitalis group the only member suitable for oral administration is digitalis itself, none other being absorbed from the alimentary canal with a sufficient degree of uniformity to render such administration satisfactory. While the infusion may be employed, either the powdered leaf or the tincture of digitalis is to be preferred. Both of these are stable, and biologically assayed potent preparations are readily available.

The absorption of either is rapid, apparently being complete within about six hours after the administration of a single dose. Occasionally specimens of good biologic activity may be encountered which are, however, rather poorly absorbed; but, in general, active preparations will be found to be absorbed fairly uniformly.

By the proper regulation of the dose it is possible to secure full digitalization by oral administration within ten to twenty hours after the beginning of treatment, and decided beneficial effects may commonly be secured within the first three to six hours. It is preferable, therefore, to administer digitalis orally in every case of advanced failure except perhaps in those uncommon instances where the condition is too urgent to wait even so short a period. The presence of nausea and vomiting due to splanchnic congestion seldom interferes with the success of oral administration in these cases. For the purpose of very rapid digitalization one may employ the body weight method which has been described recently in detail in the Journal of the American Medical Association, 1920, vol. 74, page 733. This method consists, briefly, in the calculation of the total amount of digitalis which will be required to produce full digitalization, the calculation being based upon the patient's weight in pounds, and the activity of the digitalis as determined by the cat method. The total amount required is 0.15 of one cat unit per pound of body weight, which, when determined, is then administered in four doses six hours apart, the first dose being at least one-half of the total estimated requirement; the second, one-fourth; and the remaining doses smaller fractions. While this method has proved eminently satisfactory in the hands of many, it may seem too heroic to some. It is a fact, nevertheless, that it is safer when properly carried out than is either the intravenous or the intramuscular injection of any of the digitalis bodies, and it usually yields equally satisfactory results very nearly as promptly.

Where the condition is not so urgent as to require very rapid digitalization, and for those who for one reason or another may be unable to employ the body weight method, the following plan of administration is to be recommended. By it one may fully

digitalize his patient in from one to two days: 0.4 gram (gr. vj–vij) of the powdered leaf, or 4 c.c. (dram j) of the tincture, are to be given every six hours, day and night, for four doses. The dose is then reduced by one-half and the interval is shortened to four hours, giving four doses per day and none during the night. The latter dose and interval are continued until full digitalization is secured.

Every patient should be carefully followed during the administration of digitalis in order to detect the evidences of its action and thereby to determine the effectiveness of the digitalization, since one must usually push the drug to the point of minor intoxication to secure the greatest benefit. Many criteria are available to indicate the degree of digitalization, but the following are the simplest and will generally be found to be adequate. The appearance of nausea or vomiting, except in cases of marked splanchnic congestion, is definite evidence of minor intoxication and indicates the cessation of administration, at least temporarily. In fibrillating cases the pulse deficit—the difference between the radial and apical rates—will generally be found to decline rapidly if satisfactory therapeutic effects are secured. The decline is progressive, the radial rate increasing and the apical falling until the two meet, or, more rarely, the radial rate remains about stationary while the apical declines to its level; but in either case there is a very marked reduction in the deficit, or its disappearance, which is a certain index of beneficial digitalis action. In non-fibrillating cases the appearance of partial heart-block or of premature contractions, should either develop, serves as an indication for reducing the dose of digitalis or discontinuing its administration. If instrumental methods are available, these and other criteria of digitalis action may be determined with ease and certainty, but it is only when they are fairly marked that they constitute indications of minor intoxication.

Extremely urgent cases of advanced heart failure may require the intravenous or intramuscular administration of one of the digitalis bodies, for which purpose none is superior to ouabain (crystalline strophanthin) or amorphous strophanthin. If the

patient has not previously received digitalis, an initial dose of 0.5 mg. of ouabain or 0.75 to 1 mg. of amorphous strophanthin may be injected. When the injection is made intravenously, it should be slow, consuming at least five to ten minutes. The intramuscular injection is quite as satisfactory as the intravenous and the technic is simpler, but it has the disadvantage of producing considerable local pain. This, however, may be greatly reduced if the site of the injection be massaged vigorously for about five minutes. Repetitions of not over half of the doses recommended above may be made if required, and the second dose may be given from one to two hours after the first when the latter was administered intravenously, or from two to four hours after when intramuscular. Not more than 1.5 mg. of ouabain or 2.5 mg. of amorphous strophanthin should be given during the first twenty-four hours.

Both of these drugs may be obtained in solution in ampules, but they are prone to undergo more or less rapid deterioration unless the ampules be of hard glass, or unless the solution be a "protected" one. Either drug may, however, be made into tablet triturates, in which form it will keep indefinitely.

When the patient is known to have been receiving digitalis treatment within the preceding ten days to two weeks, intravenous or intramuscular injections and the body-weight method of oral administration should be undertaken with great care on account of the danger of serious intoxication. This is due to the fact that the action of digitalis is persistent, lasting up to two weeks or more in many cases. Before resorting to any of these methods of adinistration, therefore, one should examine his patient carefully, preferably with the aid of graphic records, to determine whether or not there are any evidences of digitalis action still present. If there are none, and the case is urgent, one may proceed as already described. If, on the other hand, evidences of slight action still persist, one should avoid altogether both intravenous and intramuscular administration, and if employing the body-weight method he should reduce the amount given in the first twelve to eighteen hours to three-quarters of the total estimated requirement.

The response to the methods of treatment just outlined is usually rapid in favorable cases, and in many of those with auricular fibrillation it is little short of dramatic. Among the first clinical evidences of therapeutic effects are diminution in the patient's dyspnea and orthopnea, both of which may even disappear completely within twenty-four hours. If the patient is edematous, profuse diuresis is also often among the striking early symptoms, and it too may be evident within the same length of time. Splanchnic congestion and its attendant symptoms are also commonly relieved along with the changes just noted. In these very favorable cases, therefore, the net result of the adequate administration of digitalis is often such that symptomatic remedies may be unnecessary after the first day's treatment.

In less favorable cases the response to digitalization is slower, and even when minor toxic actions have appeared the patient's respiratory symptoms may persist, somewhat modified. It is even more common, however, for diuresis to be inadequate and for splanchnic congestion to remain but slightly altered. In such cases it is necessary to continue with symptomatic treatment and to resort to other methods of relief to be described later. As a general rule it is desirable in these cases to maintain a fairly high degree of digitalization for one or two weeks or more, controlling the amount given by the criteria previously mentioned.

In those cases which fail to respond appreciably to the adequate use of digitalis, one should also continue its administration, properly controlled, but in spite of this and the trial of such other measures as may seem indicated, the prognosis is generally highly unfavorable.

A small proportion of cases with advanced heart failure will be found in patients having high blood-pressure. So far as the use of digitalis is concerned, its existence may be disregarded, since therapeutic doses of digitalis have no direct influence upon the blood-pressure, contrary to statements so frequently made, but without supporting evidence. In those cases in which the pressure is due to advanced arteriosclerosis the use of digitalis, though it may relieve the failure of the heart, may be expected to be without influence upon the level of the blood-pressure.

In those, on the other hand, in which the elevated pressure is associated with edema, dyspnea, and cyanosis, as one of the symptoms of heart failure, the relief of the latter by digitalis is commonly followed by an appreciable and often considerable reduction in both the systolic and the diastolic blood-pressures.

SYMPTOMATIC TREATMENT

Relief of Edema.—Edema or general anascarca occurs frequently, and dietary control seems often to be of considerable value in the removal of the fluid. Although the chlorids of the urine and blood have been investigated extensively, as yet we have little definite knowledge of the rôle which they play in the development of edema in these cardiac cases, and the same is true of the subject of the mechanism of water retention. Nevertheless it is well established empirically that great restriction of the salt intake leads to rapid loss of edema through the production of diuresis in a considerable proportion of the water-logged cases. The restriction of the consumption of fluids is also of marked benefit in aiding the removal of the edema and anascarca by reducing the amount of available fluid to such an extent that little can be stored in the tissues. Neither salt nor fluid restriction should be continued for more than a week or ten days if they are not followed by a prompt reduction in the edema and an increase in the urinary output, since either restriction is capable of proving harmful if too long continued, and especially where organic renal damage complicates the cardiac failure.

The most drastic restriction which is commonly prescribed in the greatly water-logged patients of this type is the Karell diet, which is so well known that it need not be described in this place. It combines the limitation of fluid intake with the limitation of salt intake and often gives strikingly favorable results. This diet has the great disadvantage of being very distasteful to many patients and it often proves hightly irksome. It may be modified satisfactorily without sacrificing its therapeutic virtues by prescribing a total of 800 c.c. of milk per twenty-four hours with the addition of several pieces of very dry toast, zwieback, or plain crackers which may be eaten along with the milk, and on which

salt-free butter may be used. In place of either of these regimens a so-called "salt-free" diet may be prescribed, in which the total fluid intake also is limited to between 1000 and 1500 c.c. per twenty-four hours. Finally, in many cases it will be found quite sufficient to prescribe an ordinary light, semisolid diet with fluids restricted as suggested. In such a diet the use of dry toast, zwieback, and crackers to replace some of the cooked cereals, custard, junket, etc., is advisable, as this gives the patient some solid food to chew and also reduces the total fluid intake.

When dietary restrictions combined with the adequate administration of digitalis fail to reduce the accumulation of fluid in the tissues and serous cavities efforts should be made to promote fluid elimination through the kidneys or bowels. A variety of drugs have been recommended for the promotion of diuresis, but clinical experience has shown that only two are of definite value in the cases under discussion. These are the closely related xanthin derivatives, theophyllin and theobromin. Theophyllin is the more effective of the two, but it has the disadvantage of being quite prone to cause nausea and vomiting from gastric irritation. Both theophyllin (theocin) and theobromin are more effective when given during or after a course of digitalis than when used alone. Both apparently tend to fatigue the kidneys after a short time, and their administration, therefore, should be continued for only two or three days in succession, each period being followed by a few days of rest. Theophyllin should be administered in doses of 0.1 to 0.2 gram (gr. 1½–3), repeated every four hours, or 0.3 to 0.5 gram (gr. 5–8) twice daily. Any one of the soluble double salts of theobromin may be used, the dose being 1 gram (gr. 15) three or four times daily. If satisfactory diuresis follows their administration several courses should be given until the patient's edema and effusions have been removed. If, on the other hand, no diuresis follows their use in conjunction with digitalization it will generally be found that the heart failure is complicated with organic renal damage and it will be necessary to institute appropriate treatment for the latter condition as well as for the heart failure.

The alkaline diuretics have long been used in combination

with digitalis, but careful observations have shown that they are seldom of any real value. When the use of such a combination is followed by diuresis the latter is generally attributable to the action of the digitalis in restoring the circulation, not to the alkaline salts. Finally, small repeated doses of calomel, especially when used in combination with digitalis, may be tried as a means of inducing diuresis, and the combination not infrequently proves effective. The Fothergill pill (calomel, squills, and digitalis) may be used, but it is more rational and quite as effective to administer the digitalis and the calomel separately so that the dose of each may be controlled independently. This use of calomel is prone to cause salivation, hence the mouth should be watched with great care so that the administration may be stopped upon the slightest evidence of its development.

When satisfactory diuresis is not induced by these measures an attempt may be made to remove the accumulated fluid through the bowels by means of watery purgation. For this purpose the saline cathartics are the most satisfactory, since they produce copious watery evacuations without irritation of the digestive tract. Large doses should be administered in the form of fairly concentrated solutions to abstract as much water as possible, but the solutions must not be too concentrated or they will cause nausea and vomiting from gastric irritation. From 15 to 30 gm. ($\frac{1}{2}$–1 ounce) of magnesium sulphate or sodium sulphate, or half as much sodium phosphate may be given in $\frac{1}{2}$ to 1 tumbler of water as a single dose, or, preferably, slightly larger total amounts may be administered in several doses daily. The one disadvantage of such purgation in cardiac cases is the tendency it has to cause considerable depression, but it must often be employed in spite of this drawback. Not infrequently such purgation will be followed by a brisk diuresis which begins early and which often will continue after the use of the purgatives has been stopped.

Finally, when all of these measures fail to remove the effusions into the abdominal and pleural cavities, one may remove the fluid by paracentesis. While paracentesis will rarely be required for the removal of ascites in cases of heart failure, it is a matter of

common observation that pleural effusions frequently fail to be absorbed and removed by either diuresis or purgation. Further, they often cause marked interference with respiration, so that their removal must be undertaken promptly. It is, therefore, generally necessary to aspirate the pleural fluid early in the course of the patient's illness, and if the effusion is extensive this should be undertaken promptly and should be repeated if necessary. The fluid should be removed slowly; generally not more than 500 to 800 c.c. should be withdrawn at the first paracentesis of the thorax; and if the patient's cardiac failure be very grave it is well to delay the aspiration until there has been time for fairly complete digitalization to have been induced.

Respiratory Symptoms.—Dyspnea and orthopnea are frequently so intense as to demand immediate amelioration if the patient is to secure any rest whatever. For this purpose morphin is the only effective drug, and its use in this connection has already been discussed. As previously stated, the dyspnea and orthopnea are both alleviated very promptly in favorable cases by the adequate administration of digitalis, and in such cases the use of morphin need not be continued during more than the first one or two days.

The dyspnea is often accompanied by more or less pronounced cyanosis, and both are probably due in part to some degree of acidosis, or are at least aggravated by it. The administration of alkalies has, therefore, been recommended, but clinical experience seems to show that but little is to be expected from them in most cases. There is no harm in trying the alkalies, however, and in those cases in which the response to digitalis is not favorable they should certainly be administered on the chance of their reducing both the dyspnea and the cyanosis.

Cardiac Pain.—The use of morphin for the relief of the agonizing pain occasionally encountered in cases of advanced failure has been discussed, but it should be remembered that morphin is only a symptomatic remedy. The nitrites—especially amyl nitrite and nitroglycerin—are also purely symptomatic remedies, but they are often of great value in giving temporary relief from the severe paroxysmal pain of anginoid type. When the pain

is of the anginoid type they should be tried before resort is had to morphin, but if they fail, the latter drug should be given promptly.

The pain in the majority of cases of advanced heart failure is more or less directly associated with the occurrence of the failure, and relief of the latter is usually associated with amelioration or disappearance of the pain. The administration of digitalis, therefore, may confidently be expected to relieve the pain in the majority of cases in which it is capable of overcoming the heart failure. There is, however, a small group of advanced cases in which the heart failure is due to syphilitic infection, and in these there is often very severe pain associated with the presence of a more or less active syphilitic inflammation in and about the root of the aorta. This pain is relieved only by morphin and by the institution of specific antisyphilitic treatment. While the latter frequently checks the inflammatory process, it seldom has any material influence on the course of the heart failure or on the probability of its recurrence.

AFTER-TREATMENT AND PROPHYLAXIS

While the immediate relief of heart failure must always be our first aim in treatment, the value of proper after-treatment is no less great, although, its importance is not so generally appreciated. This phase of the subject is the one most frequently neglected. The first essential is the prolongation of convalescence over a period of time adequate to permit the damaged heart to regain the maximum of reserve power still left to it. When the patient has been able to assume the recumbent position without respiratory distress he should be continued in bed for at least a week after all evidences of heart failure have disappeared. At the end of this time, or longer if the conditions require, he may be allowed to sit up for a test period of not over fifteen minutes. The heart and respiratory rates should be taken before, during, and after this test period, and if there is any appreciable acceleration which does not disappear within five or ten minutes after returning to bed the patient should be given a further period of recumbency. If he responds favorably to this test, the

length of time during which he may sit up should be increased from day to day, the increase being guided by the response of his heart.

Only after the patient is able to sit up for the greater part of the day should he be permitted to begin to walk, and the same precautions should be observed at this point as when he is first allowed to rise. Upon the slightest appearance of cardiac weakness the amount of walking should be reduced or he should be forbidden to walk for a further period.

Considerable aid in restoring the heart's capacity may be gained while the patient is still confined to bed by the cautious use of massage, passive movements, and finally, graded active movements. Even, however, when the latter are well borne the patient may still be found incapable of resuming any considerable activity in the erect posture.

During the period of convalescence the patient's diet should be fairly liberal, but should be selected to avoid so far as possible any strain upon his impaired digestive functions. Liquid and semisolid diets soon become very distasteful, and nothing is gained by their use after the period of acute failure. The precise composition of the diet must be suited to the individual patient, but it is wise to allow as much latitude as possible. If edema has been a feature during the attack of failure, it is well to avoid an excess of both fluids and salt.

Patients with auricular fibrillation, and some cases of myocarditis without fibrillation, should, as a rule, be kept for an indefinite period upon the continued or intermittent use of digitalis. For this purpose the powdered leaf, dispensed in capsules, is the preparation of choice, since in this way the unpleasant taste of the drug is completely avoided. The dose must be determined for each individual patient, but will usually be found to lie between 0.1 and 0.2 gram (gr. $1\frac{1}{2}$–3) per day. Inasmuch as the action of the drug is persistent, this dose is best given once daily instead of being divided into two or three administrations. In patients with fibrillation the daily dose of digitalis should be just sufficient to keep the heart-rate (apex) at about 70 per minute. In the non-fibrillating cases the dose

should be gaged so as to be just sufficient to prevent the earliest manifestations of a returning failure.

The prevention of a recurrence of heart failure should be begun during the period of convalescence. Space does not permit a detailed discussion of this most important phase of treatment, and we must rest content with the following brief outline of the points to be considered: It should be a part of the physician's imperative duty to review the patient's life with reference to his occupation, activities, worries, and other factors which may have played an important part in precipitating the failure of his heart. With this knowledge, the physician should guide the patient's future activities so as to avoid their repetition so far as possible. The patient should be made to realize the limitations placed upon him by his heart and, if necessary, he should be urged to make a radical change in his occupation and pursuits. It should be made clear to him that if he is to enjoy a reasonable degree of comfort he can do so only at the expense of a considerably reduced activity.

In addition to the foregoing the patient should be taught to recognize at their inception the subjective symptoms which indicate overtaxation of his heart. He should be taught to heed at once the warning given him by the occurrence of slight dyspnea, of fatigue, sleeplessness, puffiness under the eyes or about the ankles, etc., and to report at once to his medical adviser. It should be made a matter of routine to have all patients in the group under discussion report to their physician regularly every three months. By insisting upon the observation of these and other injunctions it is often possible to ward off recurrences of heart failure, even in these advanced cases, for long periods of time.

CLINIC OF DR. ALBERT A. EPSTEIN

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CLINICAL TYPES OF CHRONIC PARENCHYMATOUS NEPHRITIS—THEIR TREATMENT AND RESULTS

Through the lack of a more suitable nomenclature the term "chronic parenchymatous nephritis" is ordinarily applied to a variety of renal affections. Under this heading we find grouped cases of chronic diffuse nephritis, of amyloid kidney, and cases of so-called chronic nephrosis. Although the types of cases are pathologically different, the similarity of the outstanding symptoms, namely, albuminuria, oliguria, and edema, makes them frequently almost indistinguishable. Recent investigations on the chemistry of the blood and on the urine have added much helpful information on the diseases in question, but ultimate recognition of the exact nature of the renal disease in a given case often depends upon historic facts, etiology, and a number of associated clinical phenomena.

Among the types of chronic parenchymatous nephritis which will be considered in the present discussion and illustrated by specific examples are the following:

1. The non-inflammatory type.
   (*a*) Pure form of chronic nephrosis.
   (*b*) Chronic nephrosis in association with myxedema: endocrine type.
2. The inflammatory type—diffuse nephritis.
3. Mixed type—primary nephrosis with superimposed diffuse nephritis.
4. Nephritis in association with diabetes.

THE NON-INFLAMMATORY TYPE

Chronic nephrosis is a term not really suited to the condition which it is intended to define, but for want of a better name will be used here to signify the chronic degenerative tubular nephritis. Chronic nephrosis occurs usually in relatively young persons. It is of obscure or unknown origin, and bears no relation to known

infectious diseases. In women pregnancy may stand in etiologic relationship to the condition. It is characterized by a pronounced albuminuria, with or without casts. The urine is usually free from blood elements. The blood-pressure is not elevated. At first the condition may be devoid of other gross manifestations; but, as it progresses, oliguria and edema invariably develop. Cardiovascular changes are not present unless brought about by some secondary extrarenal cause. Pallor is usually very pronounced. Subjectively the patient may complain of headaches, dyspnea, and vomiting.

From the pathologic standpoint this disease is distinct from the other forms of nephritis under consideration. In view of the fact that certain anatomic peculiarities in diseased kidneys are characteristic of different causes, it is surmised that the degenerative process in the kidneys in chronic nephrosis is due to an intoxication, because of the similarity of the lesion to that produced by certain toxins and mineral poisons. Thus, for example, an acute tubular degeneration amounting in severe instances to complete tubular destruction is produced in poisonings with bichlorid of mercury, bismuth, salts of uranium, etc. Milder forms of parenchymal degeneration frequently occur in many febrile diseases, especially diphtheria, yellow fever, and other infections. When the destruction of tubular epithelium is not sufficient to produce death, complete recovery takes place within a few weeks, as the tubules possess a remarkable capacity for regeneration. Although the kidney lesion in the acute and chronic forms of tubular nephritis may be alike, it is questionable whether the cases which are encountered clinically and which we term "chronic nephrosis" ever actually result from acute conditions of the character described above. The disease chronic nephrosis most often develops insidiously, and is frequently discovered accidentally, by chance examination of the urine, or only from the development of its later manifestations, namely, the oliguria and edema. That the lesion in the kidneys is of an advanced degenerative type has been recently proved at autopsy (Fahr).

In chronic nephrosis the albuminuria is usually very intense. The daily excretion of albumin in the urine may rise as high as

50 gm. In the earlier stages the output of urinary excretory substances may be normal, but functional tests show renal deficiency, such as retention of chlorids, of nitrogen, and diminished phenolsulphonephthalein excretion. Water retention may also occur even in the early pre-edematous stages of the disease. The body tissues are evidently capable of storing up considerable fluid before showing definitely the presence of edema. In fully developed cases the retention of chlorids and of nitrogen (as measured by the test diets) may be quite outspoken, but the blood fails to give evidence of such retention. This is particularly true in the edematous stages of the disease, and one reason for this is the increased distribution of these substances throughout the body in the water-logged tissues. This is evidenced by the fact that both in the early pre-edematous as well as in the postedematous stage (following treatment and general improvement) the nonprotein fraction of the blood is often increased.

The blood shows more striking changes in other respects. A certain degree of dilution develops which is occasionally more marked in the early than in the later stages, when fluids permeate from the blood into the tissues with great readiness. The erythrocytes become diminished in number and the hemoglobin content falls. The most marked disturbances are found in the quantity and composition of the serum proteins and also in the lipoid content. The total protein content of the serum decreases with a proportionate rise in the globulin fraction and the lipoids increase in amount. These changes may be slight at first, but become more and more pronounced as the albuminuria proceeds, particularly if the nutrition in respect to proteins is maintained at a level below that requisite for the needs of metabolism and to cover the loss incurred by the albuminuria.

Such are the usual findings in chronic nephrosis, and are illustrated by the following concrete examples:

1. **Early Case.**—M. S., male, twenty-eight years of age. Russian. Tailor by occupation. Married. Negative family history. Good habits. No venereal infections. Had pneumonia eight years before present illness, and an attack of influenza one year ago. With the exception of these two incidents patient

always enjoyed good health. Never suffered from tonsillitis or other focal infections.

Present ailment discovered on application for life insurance two months ago. Was rejected because of a pronounced albuminuria. Had no subjective symptoms other than nycturia, being obliged to rise to urinate once or twice every night. Voids urine five to six times during the day. Objectively the patient appears well nourished, although rather pale and flabby. Eyes react normally to light and accommodation. Mouth in good condition. The thyroid gland is somewhat enlarged. Lungs are negative. Heart is normal in point of size and action. There are no adventitious sounds. Blood-pressure is 130 systolic and 80 diastolic. Liver and spleen are not enlarged. Abdomen negative. Reflexes normal. Urine of a light straw color. Specific gravity 1018–1030. Daily output before treatment about 900 to 1000 c.c. Urine boils solid. Very numerous hyaline and finely granular casts. No blood elements in the urine.

P. S. P. test:	First hour	=	0
	Second hour	=	15 per cent.
	Total,		15 per cent.

Blood examination: R. B. C., 5,530,000.
Hgb., 95 per cent.
W. B. C., 9000.

Non-protein nitrogen	91.0	mgms.	per 100 c.c.
Urea	40.0	"	"
Uric acid	3.3	"	"
Creatinin	1.5	"	"
Cholesterol	300.0	"	"
Total serum protein	6.4	gms.	
Globulin fraction	50	per cent.	

We have in this patient an example of chronic nephrosis in the pre-edematous stage. Clinically he presents no evidence of abnormality other than the urinary findings, marked reduction in phenolsulphonephthalein elimination, as well as retention of water, salt, and nitrogen, as indicated by the test diet. Notwithstanding the water retention edema is not demonstrable. The cell elements from the blood do not show much deviation from the normal, in fact, a moderate polycythemia is present. Chem-

ically, however, the blood shows considerable change. We find here a marked rise in the non-protein fraction, all the other elements, other than creatinin, being increased. The cholesterol shows appreciable increase over the normal (the average figure for which is 200 mg. per 100 c.c.). The protein content of the serum is just below normal, the usual values for which are 6.5 to 8.5 gm. per 100 c.c. The globulin portion of the serum, however, already shows a decided rise, for normally this fraction does not exceed 35 per cent.

From the standpoint of the blood and the urinary findings this case could not be readily differentiated from a case of chronic diffuse nephritis. Clinically this case differs appreciably from one of the latter type, with changes in the blood and the urine of the character found in this case.

The absence of any evidence of infection, of any history of previous acute attacks of nephritis, argues against this being of the inflammatory type of renal disease. The blood-pressure is normal and the cardiovascular system shows no abnormality. Subjective symptoms are also lacking. The urine does not show any cellular elements.

Although the criteria here presented do not furnish absolute proof that this disease is one of chronic nephrosis, as contrasted with diffuse nephritis, the therapeutic test, of which I shall speak presently, and the subsequent history, justify the conclusion that this case is one of the non-inflammatory variety.

I have mentioned before that this case showed a decided tendency to the retention of water (and salt), the ultimate result of which was likely to be edema. Edema is a complication which constitutes not only a distressing symptom to the patient, but is also an indication of a much more profound disturbance in the water exchange, than merely that of failing kidney function. This disturbance is of extrarenal origin, resident in the blood, which is indirectly the outcome of the intense and continued albuminuria.

Notwithstanding the high values of the non-protein elements found in the blood, to overcome the water retention, and thus the tendency to edema (for reasons which will be stated more fully

in the discussion of the next case), this patient was put on a high protein diet, with the ultimate amelioration of all the abnormal conditions. The patient was confined to bed and put on a diet containing 60 to 100 gm. protein, 60 to 120 gm. carbohydrate, and 0 to 60 gm. fat, having a food value of 500 to 1500 calories. Closer study of the progress of this case illustrated a number of points mentioned in the foregoing general discussion of chronic nephrosis. First, that water retention occurs in the early stages of the disease without the formation of demonstrable edema. Thus we find in the accompanying table that the elimination of urine continuously observed for fifteen days exceeded by 3150 c.c. the amount of fluid ingested.

Date, 1919.	Urine, c.c.	Fluid intake, c.c.
Nov. 8	650	1000
" 9	1000	"
" 10	1350	"
" 11	1300	"
" 12	1450	"
" 13	1250	"
" 14	1400	"
" 15	1200	"
" 16	1200	"
" 17	1200	"
" 18	1400	"
" 19	950	"
" 20	1300	"
" 21	950	"
" 22	1100	"
" 23	1100	"

Hand in hand with the increased elimination of fluid a decided change also occurred in the blood, for an examination of it, made at the end of this period of observation, showed the following:

Non-protein nitrogen	78.5	mgms. per 100 c.c.
Urea nitrogen	33.0	" "
Uric acid	2.7	" "
Creatinin	1.1	" "
Cholesterol	187.0	" "

Although the non-protein fraction of the blood has not yet reached the normal level, a definite decrease is observable, and this, notwithstanding the fact that a large amount of protein food was furnished in the diet. The significance of this particular

phase of the subject will be discussed later. The protein content of the blood-serum was not determined at this point. At this period the patient was permitted to be up and about, and to resume his occupation. The food value of his diet was increased to nearly 2400 calories. Salt and fluid ingest was unrestricted. At the end of three months the blood examination revealed a composition of practically normal values. The albumin in the urine became reduced to a mere trace with casts encountered only occasionally. The general health of the patient was excellent.

Barring adventitious incidents or secondary complications to which nephritic patients are subject, the difference between an early and an advanced case of chronic nephrosis is practically only a quantitative one. The chief symptoms of a chronic nephrosis, as stated before, are the intense albuminuria, oliguria, and edema. Whereas the edema and oliguria may be lacking or slight in the early cases, they gradually become more and more pronounced as the disease advances. The quantity of urine which patients with this disease may eliminate daily may fall as low as 200 to 300 c.c. The edema extends until the entire body becomes involved. The serous cavities also become filled with fluid. The dropsy may extend to the submucous tissues, such as those of the conjunctivæ, resulting in marked chemosis. The chemical character of the fluid that accumulates in the subcutaneous and submucous tissues, as well as the serous cavities, in this disease is of very great interest, and, when compared with chemical analyses of like fluids found in other diseased conditions, aids in understanding the nature of the process which is responsible for the accumulation of fluid in the body. In fact, the chemical composition of these fluids is so distinctive and characteristic of the condition that it helps considerably in excluding the presence of factors which are likely to contribute to the development of edema, namely, static disturbances in the circulatory system, mechanical obstruction of blood flow, or effusions due to inflammatory causes.

The accompanying table shows at a glance striking differences in the comparison of fluids obtained from cases of chronic nephrosis, and those of other origin.

AVERAGE COMPOSITION OF EFFUSION FLUIDS

Serous Fluids:

	Gms. per 100 c.c.			
	Total protein.	Globulin.	Albumin.	Globulin, per cent.
Cardiac conditions.....	3.352	1.199	1.788	43.0
Hepatic cirrhosis......	3.174	1.138	1.856	41.0
Chronic nephrosis.....	0.285	0.285		100.0
Subcutaneous Fluid:				
Chronic nephrosis.....	0.098	0.080	0.018	81.0

The feature in which the dropsy fluids of chronic nephrosis differs from others is the very small amount of protein in it. It consists chiefly of water, salt, and non-protein nitrogenous substances. The latter substances are usually present in concentration similar to that found in the blood of corresponding cases. The non-protein substances (and the chlorids as well) are all relatively diffusible substances, and they become readily distributed throughout the body, as the volume of fluid retained in the body increases. This factor is of importance and explains, as stated before, the normal or relatively low content of these substances in the blood of such cases. It also throws some light on the pathogenesis of some of the symptoms which often develop in these advanced cases of chronic nephrosis and are ordinarily ascribed to uremia. The chief symptoms which are frequently so interpreted are the headaches, the visual disturbances, the vomiting, and too, the twitchings and coma. In point of fact, these symptoms are probably due to edema of the cerebrospinal system, and not to any poisoning from retained urinary substances. The true cause of the condition generally termed "uremia" is not definitely known, but comparison of the blood findings in various renal conditions indicates that uremic phenomena are associated with the retention or concentration of nitrogenous waste products in the blood. To some extent this also applies to the retention of inorganic acid salts and reduction of the alkali reserve of the blood. Retention of nitrogen waste products, in chronic nephrosis, of course, does take place in the body as a whole, but (except in the pre- and postedematous stages) concentration of these substances in the blood does not occur.

From the standpoint of etiology I have stated before that chronic nephrosis is usually of obscure origin, and that occasionally pregnancy stands in causal relation to it. The following case is one in which the renal condition developed shortly after parturition, and, although only of moderate severity, exhibited many of the conditions just mentioned.

Early Case.—L. S., admitted to Mt. Sinai Hospital, service of Dr. Libman. Thirty-two years of age. Housewife. Married ten years. Has three healthy children; the youngest being three weeks old. Had two miscarriages prior to the birth of the last two children. Cause of the miscarriages not definitely established. Menses always regular. The past history was negative with the exception of measles in childhood, and several attacks of sore throat, but no true tonsillitis. Last attack of sore throat occurred one year ago. Otherwise the patient always enjoyed good health.

The complaint for which the patient came under observation was edema of the lower extremities of three weeks' standing, traceable to a condition of like nature, which developed ten weeks before. The patient ran an uneventful course of pregnancy up to the eighth month. Her urine was examined periodically every four weeks prior to this, and had always been found normal. About this time the patient developed a slight edema about the ankles. A few days' rest in bed caused the swelling to subside. There were no other symptoms. Parturition was normal at full term, and she remained in bed for two weeks thereafter. About one week later swelling of the feet and legs developed, and she was put to bed. The examination of the urine at this time revealed a severe albuminuria. Within the next three weeks the edema progressed markedly and extended over the entire body and face. The abdomen also became very large. The patient vomited twice as a result of medication. She had no headaches or disturbance of vision at that time and no cardiovascular symptoms. The bowels were regular. Urine was diminished in amount, about 20 ounces per day, and there was no nocturnal urination.

On examination we find the patient to be suffering from a

generalized dropsy. The conjunctivæ are also moderately edematous. Pallor of the skin and mucous membranes is very marked. The hair is dry and sparse. The tongue, which is fissured, is slightly coated and moist. The heart and lungs are negative. Pulses are equal, of fair force, and moderate tension. Blood-pressure is 130 systolic and 80 diastolic. The abdomen is large and tympanitic. Signs of fluid in the peritoneal cavity are present. The circumference of the abdomen at the level of the umbilicus is 118.5 cm. Liver and spleen are not enlarged. Rest of the examination is negative. The patient's weight is 208 pounds.

The urinary output is between 200 to 500 c.c. Albumin is present in large amounts; casts, both hyaline and granular; cellular elements are absent.

P. S. P. test:	First hour	=	0
	Second hour	=	45 per cent.
	Total,		45 per cent.

We have here before us a case of a young woman suffering from an oliguria, severe albuminuria, and general anasarca. Though not definitely established, the development of the trouble seems to be in some way associated with the termination of pregnancy, which in all respects appeared to be normal. The first symptoms of which the patient became aware were the edema and oliguria. On examination she presents definite evidence of both.

At the outset the patient was put on the older accepted therapeutic régime, namely, the Karell and salt-free diets, and the employment of various diuretics, without any effect upon her condition after five weeks of this treatment. In the last week of this régime the average daily urinary output amounted to 390 c.c. The blood examination made at this time (March 2, 1918) showed the following:

Non-protein nitrogen	54.8 mgms. per 100 c.c.
Urea	21.0 " "
Total protein	4.38 gms.
Globulin	3.2 gms., or 74.5 per cent.
Cholesterol	840.0 mgms. per 100 c.c.

Compared to the degree of oliguria, the low concentration of the non-protein nitrogen in the blood is accounted for by the large distribution of these substances in the edematous tissues, as previously explained. The blood does, however, show a diminution in the protein constituents, with a preponderance of globulins and an increase in the lipoids. The latter two findings in the blood deserve particular attention because of their twofold importance; the first relates to their rôle in the pathogenesis of the edema, and the second has a special bearing on the therapeutic measures for which they serve as an indication. The retention of salt and with it of water in this type of nephritis (and their ultimate deposition in the tissues) has been ascribed to defective function on the part of the kidneys to eliminate these substances. This view was first propounded by Widal and is still firmly adhered to, and it has been claimed in consequence that the edema in such cases can be reduced by the close adherence to a salt-free diet, with the limitation of the intake of fluid. But reduction of the edema by the adoption of a salt-free diet, as already stated, has not been successful.

When an edematous case of chronic nephritis is first put to bed an increased flow of urine often may result from the rest given to the heart and the amelioration of the general circulatory conditions, but in the majority of cases the edema persists, however strictly the diet be enforced. Equally disappointing usually are the attempts to reduce edema by the use of diuretics. The experience of the above case supports this statement. Indeed, in cases of dropsy of the type described the use of diuretics is contraindicated unless circulatory disturbances are present, when diuretics of the digitalis and caffein group may be of some use; but in the absence of such disturbances their employment is worse than futile because they tend rather to lower the renal function. To reiterate, the application of the salt-free diet and the use of various diuretics (as the accompanying protocol shows) have been without any effect on the edema, albuminuria, or the general condition of this patient.

Treatment:

1918.		
Jan. 31	Karell diet	900 c.c. daily.
Feb. 2	Karell diet	1000 " "
" 6	Salt-free diet.	
" 6	Infusion of digitalis.	
" 9	Theocin.	
" 11	A. B. C. mixture.	
" 15	Oil of juniper.	
" 18	Infusion of apocynum.	
" 20	Citrate of caffein.	

Result:

Date.	Fluid intake, c.c.	Urine output, c.c.	Weight, pounds.
Feb. 1	1200	475+	
" 2	1440	650+	
" 3	1000	600+	208
" 4	1000	650+	
" 5	1000	800	203½
" 6	1000	775+	205
" 7	1000	300+	204½
" 8	1000	650	203¾
" 9	1000	750+	203½
" 10	1000	550+	201½
" 11	1000	600	202
" 12	1000	850+	203
" 13	1000	600	202½
" 14	1000	700	203
" 15	1000	550	203½
" 16	120	300+	204½
" 17	120	600	
" 18	120	500+	203½
" 19	210	250+	204¼
" 20	330	600+	202
" 21	270	510	201¼
" 22	270	375+	200⅛
" 23	270	565	199¼
" 24	270	575	199½
" 25	270	400+	199¼
" 26	270	310+	199¼
" 27	270	450+	199½
" 28	270	495+	
Mar. 1	270	295+	197½
" 2	270	175+	197½
" 3	270	250+	196½

The result was not surprising, and bore out the view that the salt retention theory of the causation of edema in this type of

renal disease is undoubtedly fallacious. This case gives striking proof that successful cure of the edema and ultimate recovery is more likely to follow the procedure based upon the view that the edema in chronic nephrosis is due to extrarenal causes, chief of which is the alteration in the blood chemistry referred to above. (See page 147.) Briefly stated, the cause of edema in this type of nephritis (Epstein) is the decreased osmotic pressure of the blood resulting from the diminution of the protein content of the blood-serum, a condition directly due to the steady loss of large quantities of albumin in the urine. The altered condition of the blood-serum (and the consequent reduced osmotic pressure) favors the absorption and retention of fluid by the tissues. Hence the great edema and oliguria.

The increased lipoid content in the blood which occurs in chronic nephrosis, and is also present in our case, indicates a state of impaired nutrition, and constitutes an additional disturbing factor in the physicochemical state of the blood. The indications for the treatment of such cases rest in the facts mentioned, and therefore are: first to increase the protein content of the blood, and thus restore its osmotic power; second, to remove the excessive lipoids. To effect this a diet is necessary which is rich in proteins and poor in fats. Starchy foods are limited in order to promote the maximum assimilation of proteins and to lessen the production and retention of water. Fat is limited to lessen the amount of lipoids. The effect of such a procedure becomes readily obvious upon examination of the data presented in the protocol of our case.

On March 4th the patient was put on a diet consisting of the following:

Water	240 c.c.
Milk (skimmed)	360 "
Coffee	180 "
Broth	220 "
Egg white	8
Cracker	1
Matzoths	1
Veal chop	1
Chicken	2 ounces.
5 per cent. vegetables	250 gms.
10 per cent. vegetables	100 "
Orange	1

All medication was stopped. Within three days after institution of this diet diuresis set in, with consequent progressive reduction of the dropsy. At the end of three weeks the patient's edema had subsided completely. The blood showed progressive improvement in its composition in respect to proteins and lipoids.

BLOOD

March 2d:	
Incoagulable nitrogen	54.8 mgms. per 100 c.c.
Urea nitrogen	21.0 " "
Total protein	4.38 gms.
Globulin	3.2 gms., or 74.5 per cent.
Cholesterol	0.840 per cent.
March 23d:	
Incoagulable nitrogen	60.5 mgms. per 100 c.c.
Urea nitrogen	14.0 " "
Cholesterol	0.424 per cent.
March 31st:	
Incoagulable nitrogen	52.5 mgms. per 100 c.c.
Uric acid	1.8 " "
Creatinin	1.4 " "
Cholesterin	0.675 per cent.
Total protein	5.2 gms.
April 4th:	
Incoagulable nitrogen	66.3 mgms. per 100 c.c.
Cholesterol	0.545 per cent.
Total protein	6.0 gms.

URINE

Date.	Fluid intake, c.c.	Urine output, c.c.	Weight, pounds.
Mar. 4	420	300+	198½
" 5	1430	200+	199
" 6	1200	450	200½
" 7	1450	350+	201
" 8	1080	850	
" 9	1200	1250	201
" 10	1000	1630	200¼
" 11	1000	1675	198¼
" 12	1000	1375	
" 13	1000	1285	196¾
" 14	1000	1525	196¾
" 15	1000	1305	194¼

Date.	Fluid intake, c.c.	Urine output, c.c.	Weight, pounds.
Mar. 16	1000	2300	192
" 17	1000	1750	
" 18	1000	2025	182
" 19	1000	2000	182¾
" 20	1000	2500	179
" 21	1000	1900	176¾
" 22	1000	2750	172¾
" 23	1000	1700	168¾
" 24	1000	2800	163½
" 25	1000	2850	159½
" 26	1000	2950	154¼
" 27	1000	3300	150
" 28	1000	2200	145½
" 29	1000	2100	142¼
" 30	1000	2300	
" 31	1000	1650	136½
April 1	1000	2200	134
" 2	840	2200	133¼
" 3	1000	250+ (lost)	132¼
" 4	1000	700	131
" 5	1000	1200	131
" 6	1500	1200	131¼
" 7	1500	1200	131¼
" 8	1500	1250	131½
" 9	1500	1800	131½
" 10	1500	2000	131
" 11	1500	2150	129¼
" 12	1500	1000	129
" 13	1500	1350	127¼
" 14	1500	1250	127½
" 15	1500	900	128
" 16	1080	1000	128
" 17	1200	1100	128¼
" 18	1500	1005	129
" 19	1208	675	129
" 20	1200	1100	129½
" 21	1350	1000	

Although the albuminuria persisted, the diet was continued, with a gradual increase in the amount of protein allowed, and also in the total food ration. On June 16th, some months later, the disappearance of albumin was noted and has remained absent ever since—a period of nearly two years. Now the elimination of urine and its general composition is normal. So, too, is the

blood. (Protein 6.5 gm. per 100 c.c.; cholesterol 180 mgm. per 100 c.c.)

It is of interest to note that the menses have also returned (May 17, 1918), although lactation was stopped many months before.

Whereas the administration of a diet such as that given this case undoubtedly helps to restore the conditions in the blood, its effect upon the ultimate recovery from the renal affection cannot be determined with certainty. In the pure forms of chronic nephrosis the ultimate result of the treatment is usually complete recovery, but if any extraneous factors exist which may have a bearing upon the prolongation of the disease itself (*i. e.*, the albuminuria) these must be removed. The nature of these extraneous factors may vary. In this particular case every vestige of the process of reproduction had to be removed because of the fact that the disease developed in the course of a pregnancy. For this reason the interruption of lactation may have had a bearing on the ultimate recovery of the patient. That this may be so is born out by the fact that the return of the menses was followed shortly by a cessation of the albuminuria. It may be of interest also to add here that the progressive loss of hair, first noted with the onset of the disease, stopped with the disappearance of the albuminuria, and the growth of hair returned.

The measures employed in the case just given, however, may be inadequate in unusually severe cases where emergency may require more drastic means to attain a successful result. This may take the form of blood transfusions. The object of this procedure is the same as that of the slower methods of feeding, namely, the restoration of the blood to a normal condition.

It was stated before that with the general advance of the disease symptoms may develop which simulate so-called "uremia," such as vomiting and coma; and, as previously explained, these symptoms are not due to the retention of toxic substances, but are the result of edema of the nervous system. As the reduction of the edema may be imperative, some relief may be obtained by tapping of the extremities, or paracentesis of the serous cavities, or even of the spinal canal, but, as a rule, this is

slight and of short duration. As long as the condition of the blood remains seriously altered the edema of various parts of the body will persist and increase. The advent of coma may interfere entirely with the necessary feeding of the case; in such instances transfusion of the blood must be resorted to. The following case serves as an example of such a procedure and its effect upon the clinical course of the disease. This case is of unusual interest both in point of development and ultimate result. It will be given in detail.

Advanced Case.—J. J., a native of Holland, twenty-three years of age, salesman, was admitted to Mt. Sinai Hospital (service of Dr. Brill) on November 10, 1915, suffering from swelling of the legs.

Family History.—Mother died of cancer of the liver; no other diseases recorded.

Personal History.—Smokes moderately, does not drink. One attack of gonorrhea four years ago. Denies syphilis.

Past History.—Patient has had no illnesses whatever except measles in childhood. Suffers frequently from coryza.

Present Illness.—Two weeks prior to admission patient noticed a swelling of the penis, which disappeared in twenty-four hours. At that time he had a sore throat. His legs were not swollen. One week later the patient began to feel tired and and the legs became swollen. The swelling increased up to the present and the swelling of the penis returned. Patient believes that he is urinating less than heretofore. Has no nycturia. No headaches. Eyesight is good. Bowels are regular.

Upon examination the patient appears pasty and anemic, with edema of the back and lower extremities. Most of the superficial lymph-nodes are somewhat enlarged. The eyes are negative, but there is edema of the conjunctivæ and puffiness of the eyelids. The mouth shows caries of the teeth. The tongue is coated. The tonsils are not enlarged. There is an alveolar abscess on the anterior portion of the hard palate from which a thick green pus exudes. (Culture of pus reveals anhemolytic streptococcus.) Chest examination shows signs of fluid in both pleural cavities, but the lungs appear to be sound. The heart is

normal in size. Cardiac impulse is not seen or felt. Action is regular and slow. Sounds are clear and there are no murmurs. The second aortic is not accentuated. Pulses are equal and regular. Blood-pressure is 110 mm. systolic and 80 mm. diastolic. There is no thickening of the arteries. The abdomen is enlarged. Slight shifting dulness in both flanks with fluid wave is present. Spleen and liver are not palpable, although the area of dulness over the latter is somewhat enlarged. Genitalia are negative. The back and extremities are very much swollen. Reflexes are normal.

The quantity of urine voided in twenty-four hours is about 800 c.c. Specific gravity of single specimens varies from 1009 to 1024. Both hyaline and granular casts are present.

P. S. P. test shows the following result:
Color appeared in sixteen minutes.

First hour.............	60 c.c. urine with 23 per cent. P. S. P.
Second hour..........	300 c.c. urine with 3 per cent. P. S. P.
Total..........................	26 per cent.

We have here a case in which the patient complains of but one definite symptom, namely, edema. The urinary examination gives evidence of marked renal involvement with decided impairment of function. The relatively acute onset of the edema, coupled with the objective urinary findings, occurring shortly after an alleged attack of sore throat, would lead one to conclude that the case is one of acute diffuse nephritis. Although the history of fever is lacking and the urine is free from blood elements, it is nevertheless difficult to draw any other conclusion. Whether the dental infection noted in the physical examination had any bearing on the production of the disease in question it is impossible to state. It is of interest to observe here that after a brief rest in bed, and without any special therapeutic measures, the urinary output increased and the edema subsided completely. The patient left the hospital four weeks later, December 6, 1915, very much improved, but with a persistent albuminuria, only to return again after an absence of two weeks (December 20, 1915) with a recurrence of the edema.

The physical examination at this time was practically the same as on the first admission. Blood-pressure was 124 mm. systolic and 86 mm. diastolic.

P. S. P. test. Color appeared in thirty minutes.		
First hour.............	45 c.c. urine.....	24 per cent. P. S. P.
Second hour...........	30 c.c. urine.....	18 per cent. P. S. P.
Total...........................		42 per cent.

Although the function of the kidneys as measured by the phenolsulphonephthalein test at this point was better than at the time of first admission, the patient seemed to grow steadily worse. Notwithstanding the restriction of fluid and salt (Karell diet for eleven days) the weight rose, the edema increased, and the patient began to complain of nausea.

The administration of diuretics and pituitrin hypodermically, as well as sweats and colon irrigations, also proved to be unavailing. The excretion of phenolsulphonephthalein dropped to 26 per cent. in two hours (January 7, 1916). The oliguria increased (daily output of urine 350 to 400 c.c.). The blood showed the following:

	Gms. per 100 c.c. of serum.					
Cell. volume, per cent.	Total protein.	Incoag. nitrogen.	Globulin.	Chlorid.	Cholesterol.	Globulin in protein, per cent.
20	3.958	0.084	2.594	0.404	1.150	66.0

Owing to the condition of the blood a phlebotomy was performed on January 18, 1916. Five hundred c.c. of blood were removed and a transfusion of 700 c.c. of blood from a healthy donor was given. This was followed by an increase in the excretion of urine which lasted only two days. A second phlebotomy and transfusion were performed one week later (January 26, 1916), with a similar result. Fluids and salts were still restricted. The general condition grew steadily worse.

On February 1, 1916 the phenolsulphonephthalein elimination was only 18.5 per cent. in two hours. The blood-pressure rose to 155 mm. systolic and 120 mm. diastolic. From this time on for the next ten days the patient's condition grew rapidly worse, showing definite signs of so-called uremia.

On the 9th of February, 1916 the following observation is noted: The patient is unconscious; breathing is deep and stertorous. The chemosis of the conjunctivæ is more marked than it has been. A phlebotomy was performed and 220 c.c. of blood were removed. A few minutes thereafter the patient had a severe generalized convulsion; at first tonic, then clonic. The left side seemed to be involved more than the right. The convulsion lasted two minutes, leaving the patient still unconscious, with small, rapid pulse, slow lateral conjugate movements of the eyeballs, and occasional nystagmus. The respirations were slow, but not labored. Blood-pressure was 145 and 100 mm. The patient remained unconscious for seven hours. Upon return to consciousness the patient was put on a high protein diet, and three days later another phlebotomy was done, followed by a transfusion of 500 c.c. of blood. At this point the blood-pressure rose to a higher level than at any previous time, 180 mm. systolic and 146 mm. diastolic. The urinary excretion, however, became increased, 800 to 1000 c.c. daily. However, the edema and chemosis persisted and the patient complained of headaches. On February 25th a paracentesis abdominis was performed and 4000 c.c. of fluid removed. Up to the time of the institution of the high protein diet all the usual measures heretofore in vogue were employed.

Since the institution of the high protein diet the patient passed noticeably larger quantities of urine, which increased progressively. On March 29th the phenolsulphonephthalein excretion test rose to 44 per cent. The blood-pressure dropped to 155 and 110 mm. The edema began to subside.

April	5	Blood-pressure, 135/100.
"	9	Only slight pretibial edema present.
"	24	Blood-pressure, 118/100.
May	2	P. S. P. test 67 per cent. in two hours.
"	9	All edema subsided. Patient, to all intents and purposes, normal. Albuminuria persists. Blood-pressure, 120.

The following is a brief synopsis of the urinary findings at different stages of the disease:

URINALYSIS

Dec. 21, 1915 to Jan. 30, 1916:
Amber; acid. Sp. gravity, 1026–1042.
Albumin ++++ and solid.
Microscopic: Many hyaline and granular casts.
Few W. B. C.

Feb. 3d to Mar. 9, 1916:
Straw color; cloudy; acid. Sp. gravity, 1028–1040.
Albumin ++; Microscopic: Many hyaline and granular casts.
Few W. B. C. and R. B. C.

Mar. 10 to 27, 1916:
Straw color; cloudy; acid. Sp. gravity, 1036–1012.
Albumin ++; Microscopic: Hyaline and granular casts.
W. B. C. and epith.

Far more striking, of course, than the above synopsis of the urinalysis are the actual quantitative estimations of the urine made from day to day, just before and after the institution of the treatment with the high protein diet.

EFFECT OF TREATMENT ON THE URINARY EXCRETION

Date, 1916.	Quantity, c.c.	Urinary nitrogen, grams.	Chlorids, grams.	Total protein, grams.	Globulin, grams.
Mar. 1...	425	4.455		17.73	3.68
" 9...	660				
" 10...	590	8.425	2.178		
" 12...	540	8.425		5.84	
" 13...	535	4.93			
" 16...	1050	5.984			
" 17...	1250	9.094		9.94	4.78
" 18...	1500	7.686	9.585	14.4	4.14
" 19...	1340	6.415	15.983	14.8	4.15
" 20...	2450	9.947	35.485	20.1	5.95
" 21...	1680	5.738	21.200	14.0	5.06
" 22...	2260				
" 23...	2000	4.200		39.2	6.65
" 24...	2300	5.345	27.434	41.2	5.88
" 25...	2100	4.645	24.154	35.6	4.48
" 26...	1900	4.096	23.474	39.9	3.34
" 27...	1420		18.349		
" 28...	2500	9.100	29.820	13.1	
" 29...	2500	8.400	27.060	9.2	3.06
" 30...	2760	9.660	27.826	4.8	2.93
" 31...	3000	9.494		12.6	5.77
April 1...	2600		27.690		
" 2...	2500		22.010		

In the earlier figures we observe some of the characteristics of the condition, namely, the oliguria and the reduced elimination of chlorids. On the other hand, the amount of protein eliminated by the kidney each day is fairly high.

The blood, too, shows the changes which were previously noted as being distinctive of the condition, namely, diminished content in the serum protein with a preponderance of the globulin fraction and an increase in the lipoids.

In discussing the rationale of the treatment of chronic nephrosis it was stated that the object of transfusions and the high protein diet is to restore normal conditions in the composition of the blood. The following tables show the effect of measures employed upon the composition of the blood.

EFFECT OF PHLEBOTOMY AND TRANSFUSION ON THE COMPOSITION OF BLOOD

	Per 100 c.c. of serum.					
Cell volume, per cent.	Total protein, grams.	Incoagulable nitrogen, grams.	Globulin, grams.	Chlorid, grams.	Cholesterol, grams.	Globulin, per cent.
20	3.958	0.084	2.594	0.404	1.150	66.0
27	4.594	0.119	3.360	0.404	0.810	73.0
33	5.275	0.108	2.887	0.404	0.765	54.0

EFFECT OF TREATMENT ON CHOLESTEROL CONTENT OF BLOOD-SERUM

Date, 1916.	Cholesterol. Grams per 100 c.c.	Remarks.
Jan. 20.......	0.625	
" 26.......	0.665	Transfusion Jan. 29, 700 c.c. blood.
Feb. 14.......		Transfusion 500 c.c. blood.
" 15.......	0.307	
" 22.......	0.610	
" 24.......		Transfusion 500 c.c. blood.
" 26.......	0.532	
Mar. 3.......	0.625	
" 20.......	0.470	
April 7.......	0.465	
June 16.......	0.320	
Oct. 1.......	0.206	

The table of the urinary composition which preceded showed the influence of the restoration of the blood upon the renal secretion. It is to be noted in the blood analyses that the non-protein nitrogen in the blood rises as the case improves. It has

been recently observed by DeWesselow and Macleod that the increase in the urea content of the blood following the high protein feeding is the cause of the improved renal function, *i. e.*, the increased diuresis. The reduction of edema by means of increased diuresis must occur via the blood. That the observed increase in the urea content is responsible for the diuresis is undoubtedly a misinterpretation of the facts. It is more likely that the increased concentration of the urea is the result of a temporary accumulation of this substance in the blood caused by the passage of the edema fluid from the tissues to the kidneys.

The advantage gained by means of the treatment described, which aims to replace the loss of protein from the blood which results from the albuminuria, and the improvement in nutrition which follows transfusion and high protein feeding, is further illustrated by the progressive fall in the lipoid content of the blood. This factor serves as the most useful guide in the treatment, indicating perseverance in the use of the high protein diet so long as the lipoidemia persists.

It is of interest to note here that the ultimate result obtained in the above case, which is one of the severest encountered, was entirely successful. Not only did the edema clear up completely and permanently, but every trace of the original renal disturbance disappeared as well after six months of treatment. In 1918 the patient was drafted into the army and shortly after discharge was accepted by a life insurance company as a desirable policy holder.

Chronic Nephrosis in Association with Myxedema.—Up to this point we have concerned ourselves with what was termed "chronic nephrosis" in its pure form. Attention was called to the fact that this disease most often develops insidiously and without any apparent cause. From the general character of the changes that occur in the blood, the response of these cases to a special form of diet, as well as the association of certain other phenomena, make it appear that some of the cases at least represent a condition which is not purely renal in origin. In other words, the problem which confronts us in some of the cases is not one of nephritis, but of a disease which has as its source a metabolic disturbance.

In discussing the etiology of chronic nephrosis it was pointed out that in women the condition is often associated with pregnancy. Attention is also called to the necessity of eliminating even possible traces of the process of reproduction (such as lactation) in order to attain a completely successful result in treatment. Although the view is generally held, and perhaps correctly, that the renal disturbance which frequently develops in the course or after a pregnancy is the result of a special intoxication, there is nevertheless room for the belief that it is a result of a dysfunction of one or more of the endocrine glands. Considerable evidence can be adduced in support of such a view. But whether this be so or not in pregnancy, cases exist in which the nephrosis is undoubtedly associated with disturbance in function of a specific endocrine gland, for example, the thyroid. We find in such cases not only the characteristic feature of a chronic nephrosis, but also the existence of a certain degree of myxedema. Such cases behave in all respects like the pure forms of nephrosis, but ultimate cure is not attained until the use of thyroid is instituted.

The following case serves as an example: S. L., female, twenty-two years of age, came under my observation in February, 1918, complaining chiefly of disability caused by extensive swellling of the lower extremities. Prior to this time the patient had been in a number of hospitals and under the care of several physicians for the same complaint.

It is worthy of note that in addition to the edema of the lower extremities the patient relates that she has been growing progressively more corpulent. Coupled with the findings which point definitely to the existence of a chronic nephrosis, we observe in the physical examination a condition which resembles closely that of myxedema.

The events which followed the institution of correct therapy revealed two important phases of the condition presented: First, the disappearance of the true (watery) edema, following the high protein diet, and the reduction of the myxedema and the total cessation of the albuminuria, following the use of thyroid extract. In the spring of 1919 (six months later) the albumin was no longer

present, and the urine was normal in all other respects and has remained so ever since. The patient has enjoyed perfect health since that time.

The rôle of the endocrine glands in the pathogenesis of chronic nephrosis cannot be defined with any degree of certainty at present. The association of hypothyroidism and myxedma has been encountered by me in several instances; but symptoms pointing to other disturbances of a similar character are not uncommon. For example, profuse loss of hair, exophthalmos, enlargement of the thyroid, and pigmentation of the skin are encountered with considerable frequency. Premature menopause is also not unusual. Such cases generally show a tendency to hypertension. This constitutes a complication which often interferes with the proper differentiation of the type of renal disease under observation. It must be remembered that the cessation of the menses is usually accompanied by the elevation of the blood-pressure under ordinary conditions, hence the hypertension need not necessarily be the result of the renal condition in such cases.

CHRONIC DIFFUSE NEPHRITIS

The absence of a high blood-pressure is characteristic of chronic nephrosis, and is one of the chief clinical features by which type of renal disease is differentiated from that of chronic diffuse nephritis. Etiologically and pathologically the latter differs strikingly from chronic nephrosis.

This is a true inflammatory process affecting the glomerulo-tubular structures, and always represents the end-stage of an acute glomerulonephritis. As such, the history of one or more attacks of kidney trouble of an acute type antedates the development of a chronic diffuse nephritis.

In the acute form diffuse nephritis is a hemorrhagic inflammation of the kidney, which commonly follows scarlet fever, or acute streptococcus angina, although it may occur unassociated with any such definite etiologic factor. In this condition both the glomeruli and tubules are damaged. The cells lining Bowman's capsule as well as the endothelium of the glomerular

capillaries become swollen and proliferate actively. In the Bowman capsule these cells may form a crescentic layer filling the whole of the capsular space. In the glomerular loops the swelling of the cell tends to obliterate the lumen of the capillaries, so that the loops appear microscopically as bloodless. This latter phenomenon is responsible in large measure for the oliguria (or anuria) which occurs in severe cases.

When at the height of the disease degeneration of the swollen and proliferated cells of the glomeruli takes place, some of the loops rupture and thereby give rise to the hematuria which is one of the most characteristic symptoms of the disease. The process is usually wide-spread, every glomerulus being more or less damaged, and every loop in each glomerulus showing the effect of the disease. A few cases have recently been reported by Volhard and Fahr, however, in which the disease was limited to foci scattered through the kidneys.

When the disease proceeds to chronicity, as a rule, every glomerulus shows the results of previous damage in a peculiar hyaline thickening of the walls of the capillary loops. Some of the loops are adherent to the parietal wall of Bowman's capsule or, when the damage has been especially severe, the adherent loops may be completely replaced by hyaline connective tissue. The convoluted tubules all show varying degrees of degenerative change due probably in large part to an impaired circulation, as most of the blood which nourishes must first pass through the damaged glomeruli. This impaired nutrition also probably renders the tubules even more susceptible to toxic influences than normally. Coincident with the parenchymal degeneration the interstitial connective tissue undergoes a more or less diffuse increase.

Where the pathologic condition has existed for some time and has been associated with secondary arterial hypertension, the renal artery and its branches may show the usual secondary arteriosclerotic changes.

The entire process is, therefore, a diffuse change: glomeruli, tubules, interstitial connective tissue, and blood-vessels being all more or less involved. This type of kidney develops almost

regularly in individuals who during life have had the clinical picture called "chronic parenchymatous nephritis with hydrops."

The pathology of this type of nephritis is given in detail because it is the form which appears to be best understood from every standpoint. Combinations of any two types may occur in the same kidney. One type of lesion may be ingrafted on another, and this is what often complicates the interpretation not only of the clinical manifestations presented by a given case but also that of the pathologic findings.

Clinically, chronic diffuse nephritis presents a number of distinctive points. The antecedent history of some infection with acute attacks of nephritis is an adjunct to the diagnosis. The development of an advanced hypertension is also important. Oliguria and edema are common features. Eye changes also are common. As in nephrosis, the albuminuria in these cases is rather intense. Casts of various descriptions are present, as are also (usually) blood-cells. Although the specific gravity of the urine may in individual instances be fairly high, the rule is, however, that it is lower than in cases of chronic nephrosis. There is also a greater tendency to fixation of the specific gravity in the urine. Nocturia is also more common in this condition.

Edema is a sequel to an oliguria, which, in turn, is the result of retention of water. Coupled with this there is deficient sodium chlorid elimination. But the retention of salt and water in this condition is of a somewhat different nature from that of chronic nephrosis, in that two distinct factors may operate in its causation. First, the changes in the kidneys may cause a reduced capacity to eliminate this substance. Second, if the albuminuria is intense and of long duration, and if the food-supply in proteins is inadequate to cover the metabolic needs and the loss sustained by the albuminuria, the blood will show secondary changes like those found in chronic nephrosis, and thus will add an extrarenal factor in the causation of salt and water retention.

The combination of these two factors accounts for the greater difficulty encountered in the management of these cases and in the alleviation of symptoms. It was already stated that the albuminuria in these cases is usually less intense than in the other

type of dropsical nephritis, and the urine is of lower specific gravity. Associated with this fact we find a greater tendency to the retention of other substances as well, particularly the products of nitrogenous metabolism, and the blood may show marked degree of concentration in these substances. Whether in consequence of this fact or not, these cases show a greater tendency to the development of definitely uremic symptoms, which often terminate the case.

The following 2 cases are given as being illustrations of the different mode of onset and development, showing also differences in the clinical findings:

Case I.—G. T., female, age twenty-four, born in the United States, came under observation suffering from headaches and generalized anasarca. A history of very frequent attacks of tonsillitis, with high fever, since childhood is given. The present condition dates back four months, and followed directly after an acute attack of tonsillitis.

The special features in this case are: Blood-pressure is 140/100 mm. The phenolsulphonephthalein excretion is less than 10 per cent. in two hours. The quantity of urine ranged between 270 to 550 c.c. daily. Albumin was present in very large amounts, also numerous casts and blood-cells. The blood chemistry showed the following:

Non-protein nitrogen	47.8	mgms.	per 100 c.c.
Urea nitrogen	26.6	"	"
Uric acid	1.8	"	"
Creatinin	1.7	"	"
Cholesterol	788.0	"	"

In view of the findings in the blood (for the reasons given under the treatment of nephrosis) this patient was put on a high protein diet, with the consequent subsidence of the edema, and a blood examination made two weeks later showed the following:

Non-protein nitrogen	52.9	mgms.	per 100 c.c.
Urea nitrogen	21.0	"	"
Uric acid	2.0	"	"
Creatinin	1.7	"	"
Cholesterol	580.0	"	"

It is of interest in this case to note the reduction of the cholesterol content, which apparently goes hand in hand with the general improvement of the case. The urinary output became increased, but the chemical and microscopic findings remained unchanged.

Case II.—S. G., female, age twenty-four, Russian, came under observation suffering from headaches, dizziness, dyspnea and cardiac palpitation, and generalized edema. The condition dated back ten weeks and followed a severe cold. A history of repeated attacks of sore throat is also present. At the time of the onset of renal trouble the patient was three months pregnant. The development of the renal trouble, according to the patient's account, necessitated abortion. Aggravation instead of betterment followed the abortion.

The chief chemical findings of interest in the case are again the increase in blood-pressure, 145/100 mm., with signs of cardiac hypertrophy. The urine examination showed findings similar to those of the preceding case. There is a generalized edema and oliguria. The patient is markedly anemic, the hemoglobin being 55 per cent. The phenolsulphonephthalein elimination amounted to 15 per cent. in two hours. The blood-examination showed the following:

Non-protein nitrogen	110.0 mgms. per 100 c.c.
Urea nitrogen	40.6 " "
Cholesterol	434.0 " "

Although the blood shows a high cholesterol (as observed in cases of chronic nephrosis), the striking feature is the value obtained for the non-protein and urea nitrogen.

Notwithstanding various therapeutic measures, the patient's condition grew progressively worse, and another examination of the blood made three months later gave the following striking values:

Non-protein nitrogen	114.0 mgms. per 100 c.c.
Urea nitrogen	60.2 " "
Cholesterol	107.5 " "
Uric acid	2.5 " "
Creatinin	2.1 " "

The full extent of the nitrogen retention that can occur in cases of nephritis with hydrops, which is not exactly represented in the blood, is shown by an analysis of the edema fluid made almost simultaneously with the last examination of the blood. Composition of the edema fluid from the legs:

Non-protein nitrogen	122.1 mgms.	per 100 c.c.
Urea nitrogen	84.0 "	"
Uric acid	3.5 "	"
Creatinin	4.5 "	"

The significance of the distribution of these substances in relation to the composition of the blood has already been discussed.

The treatment of chronic diffuse nephritis must take cognizance of the factors involved in the condition. Because of the pathologic changes in the kidneys deficient renal function plays a greater rôle in this condition than in nephrosis. Failure on the part of the kidneys to eliminate waste products may result in toxic symptoms. The problem which such cases present is threefold: first, to promote the excretory function of the kidney; second, to lessen the accumulation in the blood of toxic substances; and third, to improve the condition of the blood if changes affecting the protein and lipoid constituents are present.

It stands to reason that if any direct and determinable etiologic factor is present it must be eradicated in order to make efforts in treatment effective. In the absence of any very marked accumulation of nitrogenous waste products in the blood (if an intense albuminuria is present) the high protein diet may be used with advantage. If, however, the blood shows definite retention of these substances proteins must be restricted. The diet should consist largely of carbohydrates until the excess of nitrogenous waste products in the blood is eliminated. In these cases restriction of chlorids and water is usually also necessary. The question of the fat which should be given with the food must be judged by the lipoid content in the blood.

Medicinal means, particularly the alkaline diuretics, are occasionally of service in these cases, but frequently all efforts are unavailing.

MIXED TYPE, CHRONIC NEPHROSIS WITH SUPERIMPOSED DIFFUSE NEPHRITIS

It has been observed that the degenerative type of tubular nephritis (nephrosis) may occur both in the acute and the chronic form. The acute type is represented by the cases which result from certain toxins or mineral poisons. These cases either recover completely or progress into the diffuse or glomerulotubular type, but never go into chronicity as such. The reason for this peculiarity is not clear. Although pathologically similar, the acute and chronic forms of tubular nephritis must, after all, be of a different nature. In the actue form the changes of the kidneys are the expression of a direct toxic effect of certain agents which reach the kidney for elimination. In the chronic form the toxic agent may be of a more subtle nature and the injury more gradual in its development. If one studies closely the nature and conduct of the pure forms of chronic nephrosis, one inevitably gains the impression that it is not the morphologic change in the kidneys nor their functional disturbance which constitutes the disease itself, but rather, that a disorder, possibly of a metabolic character, is at the root of the trouble; and it is for this reason that an acute nephrosis never proceeds into the chronic form, because the latter is really a disease of totally different nature. Chronic nephrosis, at least in many instances, must be a constitutional or metabolic disease.

The possibility, of course, always exists in a case of chronic nephrosis for direct damage to the kidneys from extraneous or secondary causes, with the consequent development of inflammatory changes in the entire kidney parenchyma. In other words, a diffuse nephritis of an acute or chronic form may be engrafted on the degenerative tubular type of renal affection. The converse is also possible.

Thus the association of the two forms of nephritis can occur. and in practice is frequently encountered. It has been stated before that the chronic diffuse nephritis has many points of similarity with chronic nephrosis, and it may sometimes be next to impossible to state definitely that the two conditions are associated, unless in the course of clinical observation one sees

one type of nephritis actually become engrafted on the other. Such a course is presented in the following case: H. B., a boy of thirteen years, came under observation because of generalized edema of fourteen weeks' standing. The trouble arose spontaneously, without any apparent cause, and was not preceded by any febrile or infectious condition. The early history of the patient was irrelevant. The physical examination showed the presence of several bad teeth and of somewhat enlarged tonsils. In other respects the case presented only the evidences of the renal trouble. There was no hypertension. The urine, loaded with albumin, showed casts, but no blood elements. The phenolsulphonephthalein excretion was 27 per cent.

This patient had been under treatment by various means throughout the fourteen weeks of his illness, but excepting the initial improvement noted shortly after the onset of the trouble the condition was unchanged.

The blood-examination at this time gave the following values:

Non-protein nitrogen	45.5	mgms. per	100 c.c.
Urea nitrogen	14.0	"	"
Uric acid	2.2	"	"
Creatinin	1.1	"	"
Cholesterol	552.0	"	"

On the principles set forth in the earlier part of the discussion the patient was put on a high protein diet, with the result that the edema subsided, and he was very much improved in six weeks. The albuminuria remained.

Three months later the patient returned to the hospital because of recurrence of symptoms apparently the result of total disregard of dietary restrictions. When under observation the second time the patient developed an attack of acute tonsillitis, followed by a bronchopneumonia. During this illness the edema remained unchanged, but blood elements appeared in the urine. The blood examination gave the following result:

Non-protein nitrogen	78.5	mgms. per	100 c.c.
Urea nitrogen	51.8	"	"
Uric acid	1.8	"	"
Creatinin	1.0	"	"
Cholesterol	400.0	"	"

It will be observed that at this stage the nitrogen retention in the blood was more marked, although the cholesterol content was lower.

With the subsidence of the febrile condition the patient relapsed into the original state. Treatment based on the findings was employed, now consisting of rich carbohydrate diet in order to lessen the nitrogen retention, then again of a high protein diet to overcome the edema, with resulting improvement in the general condition.

The blood examination made three months after the preceding one gave:

Non-protein nitrogen	35.0	mgms. per 100 c.c.
Urea nitrogen	14.0	" "
Uric acid	2.4	" "
Creatinin	1.5	" "
Cholesterol	364.0	" "

a result practically normal in all respects, excepting the cholesterol, which, however, is considerably lower than it has been heretofore. The albuminuria still persists and blood elements are present from time to time. The blood-pressure so far has ranged only between 120 and 130 mm.

The above case demonstrates the manner in which a condition with all the manifestations of a chronic nephrosis changes its clinical course through the intervention of an inflammatory process in the kidneys resulting from a definite and discovered cause. It developed primarily as a definite case of chronic nephrosis with all its characteristics and yielded to the therapeutic test (high protein diet) in the characteristic way. Subsequently, through the occurrence of a tonsillar infection and pneumonia, a secondary process developed in the kidneys, which gave rise to other clinical phenomena. Therapeutic measures suitable for the first condition alone are no longer available.

DIABETIC KIDNEY

The association of albuminuria with diabetes mellitus is not uncommon, particularly in individuals of middle age with

long-standing diabetes. The albuminuria encountered in these cases is the expression now of a degenerative tubular form, at others of an inflammatory diffuse type of renal disease. The blood changes may be representative of the one or the other type of nephritis. The effect of prolonged sugar excretion and of ketonuria on the kidneys is fairly well known. Pathologically the lesion may be of one or another variety. There is one particular distinctive feature of the kidneys of diabetics, and that is the deposition of glycogen in the tubular structures.

Clinically, the cases may be like that of nephrosis or diffuse nephritis, with one striking exception, namely, the absence of edema. From the functional standpoint the kidneys may be deficient in their elimination of both chlorids and nitrogenous waste products, but water retention does not occur unless cardiovascular complications arise. The absence of edema in diabetics suffering also from "parenchymatous nephritis" is a very remarkable phenomenon. Increased diuresis, which usually accompanies glycosuria, can have nothing to do with this phenomenon, because the same condition prevails even when the patients are aglycosuric. In all probability the hyperglycemia plays a greater part in this respect. The hygroscopic action of sugar is well known, and this undoubtedly exerts a definite influence on the exchange of water between the blood and the tissues. This phenomenon also adds proof in support of the view that the loss of an adequate osmotic power of the blood can lead ultimately to retention of fluid by the tissues with the consequent formation of edema.

Hypertension is often present and may be the expression of the diabetes, the nephritis, or advancing years. That this hypertension is not always found to be of renal origin, although the presence of nephritis may be certain, is proved by the fact that control of the glycosuria is often accompanied by a fall in the blood-pressure.

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SOME PHASES OF THE CIRCULATORY DISTURBANCES OF PREGNANCY: WITH AN ILLUSTRATIVE CASE

Introduction.—To the internist the medical aspects of pregnancy present a field in which in conjunction with the obstetrician much valuable clinical research may be done. Among the manifold disturbances of pregnancy which raise medical problems none is of more interest than those affecting the circulatory system. Of this the following case is an excellent example:

Chief Complaint.—This patient is a woman of twenty, who entered the hospital January 22d, complaining of weakness and shortness of breath.

Family History.—Her father died from diabetes at sixty-one. Her mother had cerebral hemorrhage at thirty-nine. Her grandfather died from Bright's disease.

Past History.—The patient has had measles, but no other acute illness. There is no history of scarlet fever or rheumatism. There was tonsillitis at ten years, after which the tonsils were removed. She has always taken cold easily, was never robust, but was always well nourished. During childhood she could be as active as other children and had no symptoms suggesting circulatory disturbance.

The menstruation began at twelve and was normal.

Present Illness.—The patient was married in 1918, and in May, 1919 gave birth to a macerated four-month fetus. This event was preceded by one uterine hemorrhage three weeks before the labor. During the entire four months of pregnancy the patient was very uncomfortable, she "vomited all day," suffered from headache, but lost no weight, and had no dyspnea or edema. The blood-pressure was known to be very high at the time of premature labor and a milk diet was enforced.

Fifteen days after the delivery of the fetus the patient got up and went about. She was allowed to go her own way, and, being somewhat heedless and full of energy, took practically no care of herself. Her husband went into military service at this time and she was without effective family or professional surveillance after that.

During the summer of 1919 attacks of so-called asthma began. These were consistently nocturnal. The patient would waken from sleep, feel oppressed and short of breath, and have to sit up in bed with audible wheezing. These paroxysms seemed to bear very little relation to food, to effort, or locality. Apparently little attention was paid to them, since they were thought to be "asthma." They gradually became so severe, however, that in September, 1919, a physician was consulted. Arterial hypertension was discovered, also albuminuria, and a dilated heart. The condition was so disturbing to the physician that he gave a very serious prognosis. A prolonged rest in bed was enforced, during which some improvement was made, but the rest became irksome and was discontinued against advice.

The patient returned to her home in the Middle West, where the situation could not be well controlled. The patient was practically bedridden, became quite dyspneic on the slightest effort, was constantly orthopneic and edematous. She would remain in bed a few days and then be up a few days. She insisted that she could not take digitalis. The chief treatment was with morphin and bromids, which controlled the attacks to some extent. There was apparently no consistent opinion as to the condition and no well-defined plan of treatment. Under these circumstances there was no improvement and the patient was sent away for advice.

Physical Examination.—Upon admission to the Roosevelt Hospital the patient presented the following picture: A small woman, propped up in bed, querulous, irritable, and giving evidence of having had things her own way. She was dyspneic upon the slightest effort, but showed only a very slight cyanosis. The eyes were negative. The mouth showed normal tonsils. There was one crowned molar tooth not above suspicion. The

lymph-nodes were not enlarged. The thyroid was of normal size and vascularity. There was marked venous pulsation in the neck, most pronounced above the right clavicle.

The apex of the heart was in the fifth space, 5½ inches from the midsternum; the right border in the fourth space was 2 inches from the midsternum. There was a marked, diffuse, lifting apical impulse. At the apex there was a faint, blowing, systolic murmur, heard also in the axilla and back. There was also a systolic murmur of a different character over the tricuspid area. Over the pulmonary area was a distinct diastolic heard down the left border of the sternum. The pulmonary second sound was almost inaudible; the aortic second excessively loud and sharp. The arteries were slightly and uniformly thickened, but without beading. The blood-pressure was 185 systolic, 155 diastolic. Over the chest there were no signs of fluid, but numerous subcrepitant râles were present at the bases.

The liver edge was felt 3 inches below the border of the ribs, was hard, tender, but no definite pulsation could be made out. The spleen was not palpable. There were no signs of ascites. There was moderate edema of the hips, sacral region, and thighs.

The temperature was persistently subnormal, ranging between 97° and 98° F.

Laboratory Data.—The urine was acid in reaction, had a specific gravity of 1030, showed a trace of albumin, no glucose; urates and a few leukocytes.

The phenolsulphonephthalein elimination in two hours was 50 per cent. The Mosenthal test-meal on admission gave the following figures:

Time.	Volume, c.c.	Specific gravity.	NaCl.	
			Per cent.	Grams.
8–10	215	1.015		
10–12	100	1.010		
12– 2	65	1.012		
2– 4	70	1.011		
4– 6	180	1.015		
6– 8	200	1.010		
Total day,	830	1.016	.64	5.30
Night,	450	1.020	.42	1.89
Total,	1280			7.19

Blood: (1) Morphology: The hemoglobin was 70 per cent.; the red cells were 3,744,000; the leukocytes, 18,800; the polymorphonuclears, 88 per cent.

(2) Chemistry: January 26th the blood analysis showed:

Non-protein nitrogen	31.70	mgms. per 100 c.c.
Urea nitrogen	13.80	" "
Creatinin	0.98	" "
Uric acid	3.90	" "
Sugar	0.10	" "
CO_2	55.50	volumes per cent.

The second Mosenthal test-meal, January 27th, gave the following result:

Time.	Volume, c.c.	Specific gravity.
8–10	30	1.015
10–12	20	1.015
12– 2	35	1.016
2– 4	20	1.017
4– 6	185	1.008
6– 8	35	1.015
Total day,	325	1.010
Night,	250	1.015
Total,	575	

February 13th chemical examination of the blood gave the following result:

Non-protein nitrogen	31.10	mgms. per 100 c.c.
Urea nitrogen	13.50	" "
Creatinin	0.95	" "
Uric acid	2.30	" "
Sugar	0.90	" "

Diagnosis.—The diagnosis upon admission was cardiac dilatation with insufficiency of the mitral, tricuspid, and pulmonary valves; arterial hypertension; congestion of lungs and liver; moderate anasarca.

Treatment.—The patient was given a salt-free diet with restriction of fluid intake to 1200 c.c. in twenty-four hours. Digitalis in the form of digipuratum, 1½ gr., was administered three times each twenty-four hours. This was alternated with periods of three or four days of the Karell diet consisting of 1 quart of milk in twentyfour-hours and nothing else in the way

of fluid or solids. An occasional dose of diuretin, 10 grs., was given to encourage diuresis.

The pulse-rate was maintained at between 60 and 80 with sufficient doses of digitalis. To assist in preserving morale, at intervals of about four weeks, the patient was allowed to "break training" and for forty-eight hours given an ordinary diet without medication.

Progress.—The result of this therapy was very satisfactory. During the first month there were no attacks of paroxysmal dyspnea, the orthopnea greatly lessened, and by March 1st the patient could sleep without having the head raised. The anasarca gradually disappeared and the patient's strength and spirits returned. The pulse-rate, averaging 100 at the time of admission, gradually declined, so that in two weeks it reached an average of 84 per minute. Under digitalis this became as slow as 60 per minute and the expected coupled beats appeared as an indication of a sufficiency of this drug.

The area of cardiac dulness diminished in size, the apex gradually assuming a position in the fifth space 4½ inches from the midsternum and loosing a considerable amount of its heaving character.

The right border by March 1st was 1 inch from the midsternum in the fourth space. By this date all murmurs had disappeared and have not since returned.

The blood-pressure readings on various dates were as follows:

January 28th, 185, systolic; 155, diastolic.
February 8th, 148, systolic; 138, diastolic.
February 11th, 148, systolic; 130, diastolic.
February 13th, 138, systolic.
February 17th, 140, systolic; 118, diastolic.
February 18th, 134, systolic; 98, diastolic.
February 20th, 154, systolic; 85, diastolic.
February 23d, 152, systolic; 98, diastolic.
February 24th, 124, systolic; 86, diastolic.
February 25th, 114, systolic; 80, diastolic.
February 26th, 122, systolic; 82, diastolic.
February 27th, 124, systolic; 87, diastolic.

February 28th, 122, systolic; 86, diastolic.
February 29th, 116, systolic; 82, diastolic.
March 1st, 116, systolic; 80, diastolic.
March 2d, 118, systolic; 80, diastolic.
March 3d, 120, systolic; 82, diastolic.
March 4th, 120, systolic; 84, diastolic.
March 5th, 124, systolic; 85, diastolic.
March 6th, 128, systolic; 90, diastolic.
March 8th, 137, systolic; 108, diastolic.
March 9th, 135, systolic; 110, diastolic.
March 10th, 134, systolic; 108, diastolic.
March 11th, 132, systolic; 100, diastolic.
March 13th, 137, systolic; 100, diastolic.
March 14th, 145, systolic; 106, diastolic.
March 15th, 152, systolic; 114, diastolic.
March 16th, 130, systolic; 100, diastolic.
March 17th, 120, systolic; 97, diastolic.
March 18th, 128, systolic.
March 19th, 134, systolic; 102, diastolic.
March 20th, 130, systolic; 94, diastolic.
March 21st, 138, systolic; 100, diastolic.
March 22d, 138, systolic; 105, diastolic.
March 23d, 136, systolic; 106, diastolic.
March 24th, 132, systolic; 104, diastolic.
March 25th, 138, systolic; 104, diastolic.
March 26th, 138, systolic; 104, diastolic.

March 10th she was allowed out of bed and gradually began to take a few steps. By March 15th she was walking about the hospital with an excellent response on the part of the heart to exercise. She was then allowed to go out in a motor and walk somewhat out of doors. March 26th she left the hospital, able to walk without dyspnea and without undue pulse acceleration. At this time there were no symptoms of cardiac insufficiency.

The liver had receded beneath the costal margin and there was no edema.

March 26th the patient left the hospital in comfort and without signs and symptoms of cardiac insufficiency.

Reporting from time to time as an ambulant patient there has been no material change in condition. The area of cardiac dulness, the pulse-rate, the response to exercise, and the blood-pressure have been practically unchanged. The blood-pressure is, however, somewhat labile. The average has been 140 systolic, 100 diastolic; but at times after any undue exertion or excitement it has reached a maximum of 170 systolic, 120 diastolic.

A survey of the renal function April 30, 1920 gave the following figures; Mosenthal test-meal:

Time.	Volume, c.c.	Specific gravity.	Urea.	NaCl.	
				Per cent.	Grams.
8–10	250	1.010			
10–12	130	1.018			
12– 2	45	1.025			
2– 4	60	1.026			
4– 7	50	1.025			
7–10	55	1.025			
Total day,	590		5.90	.56	3.30
Night,	170		3.99	.40	0.68
Totals,	760		9.89		3.98

Day specimen negative for sugar, albumin, indican.

Night specimen a faint trace of albumin, negative for sugar and indican.

Vaginal epithelium, with mucous and amorphous urates, white blood-cells, and red blood-cells (occasional).

No casts or crystals seen in either day or night specimens.

Blood urea	5.6	mg. per 100 c.c.
Blood uric acid	3.65	" "
Blood-sugar	1.66	" "

Wassermann reaction negative.

Since leaving the hospital the chief dietary restriction has been salt and animal food containing an excess of nuclein—as sweetbread, liver, kidneys, etc. Salt restriction appears to bring reward in the way of fall in blood-pressure, this substance seeming to be the chief peccant influence in the production and maintenance of periods of arterial hypertension.

General Comments.—The importance of cases of which this is a type is great. If the etiology is in many details obscure, the recognition is not difficult and the treatment often so satisfactory in results that the condition perhaps merits more study than almost any other of the medical complications of pregnancy.

Had we the opportunity to observe this woman from the onset of her trouble the following events would doubtless have come under our eye following the establishment of pregnancy. Nausea and vomiting—most marked in the morning, later weakness; exertional dyspnea, perhaps headache, increased pulse-rate, gradual onset of arterial hypertension; then albuminuria, uterine hemorrhages, fetal death, increasing toxemia, and spontaneous abortion. In a series of cases of this kind the rate at which these symptoms might develop would vary, some running the gamut within four months, as in the case under discussion; others reaching term before serious events took place. Some, again, would not develop beyond the stage of increased pulse-rate with moderate hypertension; others advance to the end stage of fetal death and a marked circulatory disturbance, ending in cardiac insufficiency and anasarca.

In a consideration of etiology we encounter some known and many unknown factors. To state that the cause is pregnancy is but to state the problem. It is true that many of these patients have what might be called an arteriosclerotic inheritance, with generations of urban ancestors and an environment in which responsibility and strain are ever present. Many habitually exhibit that lowered threshold of response to stimuli that we associate with certain types of thyrotoxicosis. Of this a somewhat labile blood-pressure is a common feature. The average blood-pressure is found to be in the higher normal ranges and the diastolic readings often tend to be rather above the normal. Repeatedly what we recognize clinically as nephritis is not a demonstrable factor. Albuminuria, casts, retention of the end-products of nitrogenous katabolism are not essential antecedents of the syndrome described, although it is true that in many the percentage of uric acid of the blood is somewhat above the nor-

mal. No study of the capacity of these patients to excrete salt in the prepregnancy period is, to my knowledge, on record. That the disturbance is immediately excited by pregnancy is definite. We do not, however, know just what upsets the equilibrium—whether it is the added burden of fetal circulation, or of the excretion of fetal katabolic products, a disturbance of endocrine balance, or the increase in blood mass which characterizes pregnancy. Singly or in combination these and other factors may play a part.

One cannot, however, escape the impression that factors largely physical are predominant. We have observed the effect upon the cardiovascular system of large, vascular uterine tumors, of which cardiac hypertrophy, arterial hypertension, and comparative tachycardia are not uncommon companion findings, and ones that may vanish after removal of the tumor with its masses of vascular channels. This suggests that the mechanical effect of a great enlargement of the blood-stream bed is not negligible. Rowntree found the blood volume was constantly increased in pregnancy. It may be that with or without a defect in the elimination of salt and of water, with or without a toxemia or endocrine imbalance, the added strain of the uterine and fetal circulation upon myocardium and vasomotor system results in the case of individuals with poorly poised circulatory equilibrium in a disturbance of circulatory balance which finds its extreme expression in a case such as we here exhibit. The dilated heart with insufficiency of mitral, tricuspid, and pulmonary valves, the arterial hypertension with extraordinarily low pulse-pressure, the general anasarca, and recurring pulmonary edema all bespeak a profound loss of circulatory equilibrium. We may visualize this heart dilated, unable to empty itself with systole, blood-vessels overfilled, yet with a spastic vasomotor mechanism and probably a relatively static blood content; the tissues water logged from stasis in blood and lymph channels, the viscera swollen with retained fluid like saturated sponges, and kidneys failing of their normal function because of this capillary stasis.

In such a condition the vicious circle is wide and complete.

To be satisfied with the term "nephritis" as a label for this syndrome is to see but a small segment of the circle, is to close our eyes to wide-spread all-embracing disturbance of fluid volume, fluid distribution, fluid mobilization, and fluid excretion. Bound up with the problem of fluid is that of salt. The rate of the excretion of chlorids and of other salts and their concentration in the plasma would be of interest and probably illuminating.

Further than this we may not at present go in our speculation as to the nature of the etiology. With therapy, however, we may with profit deal in detail. Prompt recognition and suitable management promise much. The principles of treatment are simple. The immediate cause—the pregnancy—is commonly removed by spontaneous labor, usually preceded by placental hemorrhages. Termination of the pregnancy by art is seldom required, but in those patients with advanced cardiac insufficiency, pulmonary edema, or extreme hypertension, induction of labor might be indicated. If the condition were such that the strain of labor boded ill, a rapid cesarean section might be judged preferable to the more prolonged strain of labor.

With delivery the obligation of the physician is by no means discharged. A long course of observation and of care must follow. Upon this the health of the patient and length of life may directly depend.

The restoration of circulatory equilibrium is, of necessity, a slow process and may not always be capable of accomplishment. Response to dehydration therapy and digitalization is usually gratifying. Pulmonary edema is the real emergency of the condition. The opinion of Welch that pulmonary edema is due to a disproportion between the working power of the ventricles, with the right more efficient than the left, finds a measure of substantiation in cases of this character. It would appear that the left ventricle is subjected to a greater degree of stress than the right in maintaining the fetal circulation and in working against the arterial hypertension. Toxic injury to the myocardium may be yet another factor. The result is dilatation, which may be sudden or gradual, but which is demonstrable clinically in the widened area of cardiac dulness, in the heaving apex im-

pulse beyond its former site, and usually in a musical systolic murmur maximal at the apex and denoting mitral insufficiency.

Such a ventricle probably does not empty itself completely with systole. The result is a lack of the usual "bailing out" of the lungs which, with continued efficient action on the part of the relatively unaffected right ventricle, results in capillary distention and damage, with transudation. When one meets with orthopnea, cyanosis, cough with frothy or pinkish serous sputum, musical and moist râles distributed all over the chest—a picture so often erroneously called "asthma"—there are a number of measures of value, some of which should be taken without delay. If venous pressure is high and the symptoms alarming a vein in the elbow may be opened and 12 to 18 ounces of blood allowed to escape. It is known that the withdrawal of smaller amounts does not sufficiently influence venous pressure. This measure is at times life saving and accomplishes the immediate reduction in blood volume which is the most important object in treatment. During such attacks the blood-pressure is found to be high, the heart rapid, dilated and laboring. Nitroglycerin, $\frac{1}{100}$ gr., given on the tongue every five minutes for several doses in conjunction with morphin, $\frac{1}{4}$ to $\frac{1}{2}$ gr., are often sufficient to bring relief without venesction. If an immediate digitalization seems desirable, and only then as an emergency measure, strophanthin, 0.0005 gm., may be injected into a vein and repeated in two to four hours. If much digitalis has previously been administered or if advanced arteriosclerosis is present strophanthin given by this method is dangerous and has been followed by sudden death.

The Eggleston method of giving digitalis is valuable. Approximately 15 c.c. of the tincture are given for each 100 pounds of body weight—one-half being administered at once and half the remaining amounts at six-hour intervals, so that the entire amount is administered within twenty-four hours. As a rule, the response to digitalis is prompt, and the pulse-rate can be reduced to 60 to 70 a minute and maintained at that point by either continuous or intermittent administration.

The diet should have a fluid content limited to 1200 or 1500

c.c. in twenty-four hours; otherwise the kind of food given may conform to the patient's taste and digestive capacity, with the exception that it must be strictly salt free. As a measure promoting dehydration nothing equals the so-called Karell diet. This consists of 4 glasses of milk in twenty-four hours without other intake of fluid or solid. Thirst, which is troublesome during the first forty-eight hours, may be mitigated by allowing the pulp of orange or grape-fruit, cracked ice, or chewing gum. This diet, when given with full doses of digitalis for three to five days, is followed by a profuse diuresis which continues from two to three days. Often this diuresis can be hastened by a daily dose of theobromin sodium salicylate, 10 gr. The Karell diet may be repeated at intervals of ten days until all signs of anasarca have vanished. In the periods between the diet must be limited in its fluid content to 1200 c.c. and must be free from salt.

What is the ultimate outlook in cases of this character? While many achieve a heart of apparent normal size and a normal blood-pressure, I believe that the majority show impaired myocardial reserve and a blood-pressure, if not high, at least tending toward the higher ranges and with an exaggerated response. In other words, the foundation of chronic hypertensive cardiovascular disease is laid with all the future menace of cardiac insufficiency, or cerebral hemorrhage or arteriosclerotic nephropathy.

While further pregnancies need not be interdicted, the risk of fixing the circulatory disturbance upon the woman is one not to be lightly considered. During subsequent pregnancies the constant supervision of a competent internist is advisable. Careful watch of the entire cardiovascular and renal system is demanded. By adopting appropriate measures to combat excessive blood volume, cardiac dilatation, arterial hypertension, or renal insufficiency in their incipiency much may be accomplished.

The duty of the obstetrician is not complete with the delivery of these women. Unless he has time, training, and facilities for detailed observation and careful management of the circulatory disturbance, the subsequent care of patients of this type is appropriately given into the hands of the internist.

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THE PREVENTION AND SERUM TREATMENT OF LOBAR PNEUMONIA

The Prevention of Lobar Pneumonia; Prophylactic Vaccination Against Pneumonia; Serum Treatment of Lobar Pneumonia; Method of Serum Administration; Reaction to Antipneumococcus Serum; General Discussion of the Subject.

PNEUMONIA is today the most serious infectious disease which confronts the practitioner. The mortality rate for pneumonia in the United States is now higher than that for tuberculosis and it appears to be slowly increasing every year. Pneumonia is usually divided into two groups, lobar pneumonia and bronchopneumonia. Lobar pneumonia is the more important disease economically, for the reason that it attacks young and active individuals in the prime of life. Bronchopneumonia is usually a secondary or terminal infection and occurs most commonly in infants and the aged. It is also frequently seen in connection with epidemics of other respiratory diseases, such as measles and influenza. The present discussion has to do entirely with lobar pneumonia of the pneumococcus type. Lobar pneumonia is occasionally caused by other micro-organisms, more particularly Friedländer's bacillus, but a very large percentage of the cases are due to some type of pneumococcus.

It is not necessary at the present time to go into a discussion of the various types of pneumococcus. It is perhaps worth while to note, however, that the so-called "fixed types" of pneumococcus, that is, Types I, II, and III, produce, as a rule, the more virulent forms of pneumonia and are the cause of about

75 per cent. of all cases in ordinary times. Type IV pneumonia is usually a mild form of the disease, with a mortality rate varying from 10 to 15 per cent. During the influenza epidemic Type IV pneumonia was very prevalent and the mortality rate often ran considerably higher, probably on account of the greatly reduced resistance of the patient.

The Prevention of Lobar Pneumonia.—The older conception of pneumonia attributed the disease to auto-infection of the patient with his own pneumococcus. It has been known for a long time that most healthy mouths harbor a pneumococcus and it was assumed that when an individual was stricken with pneumonia, he had become infected with his own strain, following some temporary lowering of his vitality. According to this idea, pneumonia was not in any sense a contagious disease. The discovery, however, of various types of pneumococcus led to a more careful study of the epidemiology of pneumonia, and the work of Dochez and Avery, and Stillman at the Rockefeller Institute has shown that whereas, pneumococci can be demonstrated in about 50 per cent. of normal mouths, it is quite unusual to find pneumococci of Types I and II in the mouths of healthy individuals, except where they have been exposed to a case of pneumonia caused by one of these types. Stillman has shown that the nurses and other attendants who come in contact with a case of pneumonia frequently pick up a virulent organism from the patient and become carriers, in this way disseminating the organism to other people. Furthermore, it has been shown that the pneumococci most frequently found in the mouth secretions of healthy individuals (Types III and IV) give rise to a minority of the cases of lobar pneumonia. On the other hand, Types I and II cause a majority of the cases of lobar pneumonia, are of high virulence, and are seldom found in the mouths of normal individuals except where they have been in contact with cases of lobar pneumonia. This seems to show that lobar pneumonia due to Types I and II does not arise from infection with a pneumococcus which is habitually carried in the mouth, but that infection with these organisms occurs from without.

In view of these epidemiologic studies, it is necessary for us to look upon pneumonia as a contagious disease, and to treat it as such in the hospital and in the home. Cases of pneumonia should be isolated and every precaution taken to prevent the spread of the organisms by means of carriers. The sputum should be sterilized and everything that comes in contact with the patient should be subjected to the same treatment. A careful examination should be made of all attendants and some method of mouth sterilization practised on those who carry virulent pneumococci. The treatment, in other words, should be similar to the modern treatment of typhoid fever and other communicable diseases.

It is quite obvious that many difficulties will be encountered in the practice of such a regimen. Indeed, the control of respiratory diseases by hygienic and sanitary measures is one of the most difficult problems confronting the public health officer. In view of this fact, it is natural that attention should have been turned of late to the possibility of some form of prophylactic vaccination against pneumonia. Such a course was all the more rational in view of the conspicuous success of prophylactic vaccination against typhoid fever.

Prophylactic Vaccination Against Pneumonia.—A. E. Wright was the first to attempt vaccination against pneumonia. His experiments were carried out on mine workers in South Africa. At that time, however, he had no knowledge of the various types of pneumococcus and his results were therefore inconclusive. A few years later Lister, also working in South Africa, determined the types of pneumococci prevalent in that country and prepared a vaccine from his types A, B, and C. Lister's types B and C correspond to our Types II and I respectively. His Type A has not been encountered in America. Lister vaccinated the workers in three different mines, and observed the vaccinated men over a period of six to twelve months. In one of the mines, every case of pneumonia that developed among the vaccinated men was studied bacteriologically and the type of pneumococcus determined. No cases of the types against which the men had been vaccinated developed during the period of

observation. Lister used rather large doses of vaccine (6,000,000,000 to 8,000,000,000 pneumococci in each injection), but reported no unpleasant effects from the inoculations. During the winter of 1917–18 prophylactic vaccination against pneumonia was undertaken on a large scale at Camp Upton, New York, by the writer in collaboration with Dr. Harold Austin of the Rockefeller Institute. Pneumonia became prevalent in this camp as early as December and was found to be practically all of pneumococcus origin. It was decided to prepare a pneumococcus vaccine of Types I, II, and III in approximately equal parts and to inoculate about half of the camp with this vaccine. Altogether, 12,519 men were vaccinated (about 40 per cent. of the camp strength), most of the men receiving three and four subcutaneous inoculations at intervals of from five to seven days. The total dosage was 6,000,000,000 to 9,000,000,000 pneumococci. The local and general reactions were generally mild, but in 152 cases small sterile infiltrations developed at the site of the injection which appeared to be an expression of pneumococcus hypersusceptibility. These sterile "abscesses" caused us some anxiety, but none of them proved serious and they usually disappeared spontaneously without rupturing through the skin. It was our opinion that most of them could have been avoided by injecting the vaccine a little deeper beneath the skin.

The results of pneumococcus vaccination at Camp Upton were highly satisfactory. The men were under observation for ten weeks following vaccination and during that time no cases of pneumonia of the three fixed types occurred among the men who had received two or more injections of vaccine. In a control of approximately 20,000 men, there were 26 cases of pneumonia of Types I, II, and III pneumococcus during the same period. Strangely enough, the incidence of pneumococcus Type IV pneumonia and streptococcus pneumonia was much less among the vaccinated troops than among the unvaccinated troops. The final figures showed only 17 cases of pneumonia of all types occurring among 12,519 men who received vaccine, whereas among the unvaccinated troops during the same period there was a total of 173 cases of pneumonia of all types. For

the ten weeks during which the men were under observation the pneumonia death-rate for vaccinated troops was only 0.83 per 1000; for the unvaccinated it was 12.8 per 1000.

In spite of the successful results obtained at Camp Upton, there were certain objections to pneumococcus vaccine which interfered somewhat with its extensive application. The fact that three injections were necessary in order to obtain a satisfactory immunity made pneumococcus vaccination a burden to regimental surgeons and to the men themselves, who had already received typhoid and small-pox vaccine. Another objection to pneumococcus vaccine was the occurrence of the small sterile infiltrations at the site of inoculation in about 1 per cent. of the cases.

The next experiment with pneumococcus vaccine was undertaken with Dr. Henry F. Vaughan at Camp Wheeler, Ga., the following autumn. This camp was selected because of its very high pneumonia death-rate. The experiment at Camp Wheeler differed from the Camp Upton experiment in the following particulars:

1. Pneumococcus lipovaccine was substituted for the saline vaccine which had been used at Camp Upton. This vaccine was furnished by the United States Army Medical School and the dose was 30,000,000,000 pneumococci—10,000,000,000 of each of the fixed types suspended in 1 c.c. of cottonseed oil. Only one injection was given of this vaccine and the reaction was somewhat less severe than that caused by the saline vaccine. Only five sterile abscesses developed among the 13,460 men vaccinated.

2. The troops at Camp Wheeler were mostly raw recruits of rural origin, many of them negroes. They were, therefore, less suitable as subjects for an experiment than were the men at Camp Upton who had come chiefly from New York City and were well seasoned at the time of vaccination.

3. The situation at Camp Wheeler was further complicated by the influenza epidemic which arrived shortly after the experiment was instituted, and swept over the camp before the vaccine could achieve its effect.

Altogether, 13,460 men were vaccinated at Camp Wheeler against pneumonia, a number which represented about 80 per cent. of the entire camp strength. The vaccinated men were under observation from two to three months after the injection. During this period there were 32 cases of pneumonia of pneumococcus Types I, II, and III origin among the vaccinated men and 42 of the same types among the unvaccinated. Most of these cases of Types I, II, and III pneumonia developed within the first week after arrival at camp, that is, before the vaccine had established an adequate immunity. The duration of the interval between vaccination and immunity has been determined by Whitmore and Fennel who found by experiments on rabbits that protective substances do not begin to appear in rabbit serum until the eight day after injection of pneumococcus lipovaccine. The weekly incidence rate for pneumonia among the vaccinated troops was conspicuously lower than that for the unvaccinated troops; furthermore, the incidence rate for the period of the experiment was twice as high for unvaccinated recruits as for vaccinated recruits and seven times as high for unvaccinated seasoned men as for vaccinated seasoned men. Influenza caused a marked reduction in the resistance to pneumonia even in vaccinated troops. Of the 155 cases of pneumonia of all types occurring one week or more after vaccination, 133 were secondary to influenza. The death-rate for 155 cases of pneumonia that developed among vaccinated men one week or more after vaccination was only 12.2 per cent., whereas the death-rate for 327 cases of all types that occurred among unvaccinated troops was 22.3 per cent. The death-rate for primary pneumonia among vaccinated troops was 11.9 per cent. Among the unvaccinated it was 31.8 per cent., almost three times as great. Altogether, there were 363 cases of pneumonia (all types) during the period of observation among the vaccinated troops and 327 cases among the unvaccinated. In other words, the actual number of cases of pneumonia was about the same in the two groups, though the vaccinated group represented 80 per cent. of the camp strength. A very large percentage of the cases in both groups were pneumococcus Type IV pneumonias.

It is apparent that the results of pneumococcus vaccination at Camp Wheeler were not so striking as those obtained at Camp Upton. This difference is probably due to several causes: First, it has recently been shown by Lewis and Dodge that typhoid lipovaccine has less antigenic power than typhoid saline vaccine, and the same may be true in the case of pneumococcus vaccine. It is possible, therefore, that if saline vaccine had been used at Camp Wheeler better results would have been obtained. The influenza epidemic introduced an unexpected complication into the experiment, greatly lowering the resistance of the infected men to pneumonia. Moreover, as pointed out above, we had vaccinated the troops against the three fixed types of pneumococcus, whereas the epidemic consisted very largely of pneumococcus Type IV and streptococcus pneumonia. The men had therefore been immunized against bacteria which played only a small part in the epidemic. Another important factor was the difference in personnel. At Camp Upton the men were well seasoned and in splendid physical condition. At Camp Wheeler we were dealing with undernourished and poorly developed country boys, many of whom were negroes.

It will be observed that the investigations on pneumococcus vaccine which have been carried out up to the present time have depended for their evidence in large part upon statistics. After the experiment at Camp Wheeler, it seemed very desirable that some experimental studies should be undertaken to determine the value of pneumococcus vaccine on animals. It happens that the monkey is highly susceptible to pneumonia, and we were fortunate in being able to secure a large number of Phillipine monkeys for an experimental investigation of pneumonia at the Army Medical School in Washington. Dr. Francis G. Blake collaborated with me in this study and the results have been published recently in the Journal of Experimental Medicine. In the original experiments with pneumococcus vaccine it was found that the subcutaneous inoculation of monkeys with pneumococcus Type I vaccine in doses comparable to those employed in men did not protect them completely against subsequent attacks of pneumococcus Type I pneumonia. Vaccination,

however, did modify the course of the disease. Invasion of the blood-stream by pneumococcus in vaccinated monkeys was usually slight or entirely absent, and the proportion of recoveries was considerably higher among vaccinated than among unvaccinated monkeys. On the other hand, the subcutaneous injection of small doses of living pneumococcus Type I vaccine stimulated in monkeys a degree of active immunity sufficient to protect them completely against experimental pneumococcus pneumonia of homologous type. Vaccination with living cultures, however, proved to be a dangerous procedure, as in some instances it caused a fatal pneumococcus septicemia.

Some recent experiments (not yet published) with killed pneumococcus cultures have shown that three large injections of pneumococcus saline vaccine administered subcutaneously confer sufficient immunity to protect the monkey against a subsequent pneumonia of the same type. Three small intravenous injections will accomplish the same results. These experiments afford a rational basis for prophylactic vaccination against pneumonia. The dosage necessary to immunize monkeys against pneumonia is probably larger than man could tolerate with comfort, but, on the other hand, the monkey is more susceptible to pneumonia than man and would, therefore, require larger doses of vaccine.

The question naturally arises as to how much use can be made of pneumococcus vaccine in civil life. Vaccination against pneumonia will unquestionably come into general use as the vaccine itself is improved and our knowledge of pneumonia becomes more exact. In addition to its obvious indication in army training camps, pneumococcus vaccine could be used with advantage under the following conditions:

(1) In large institutions such as insane asylums and orphanages the use of pneumococcus vaccine would probably lower the incidence rate of pneumonia which is often quite high. An experiment with pneumococcus vaccine is being carried out at the present time by the United States Public Health Service in the insane asylums of New York State and Massachusetts, which should give some very interesting results.

(2) It might be desirable for nurses and physicians who are

being constantly exposed to pneumonia in hospital wards and in private practice to receive pneumococcus vaccine.

(3) There are certain groups of industrial workers who should be vaccinated against pneumonia, such as miners, stone-cutters, etc. Firemen, policemen, and others who are constantly exposed to cold and wet should also receive pneumococcus vaccine.

(4) In epidemics of respiratory diseases, especially influenza, pneumococcus vaccine should be used to prevent the occurrence of the severer forms of pneumonia. Many of these cases will probably contract pneumonia in spite of the vaccine, but if the fixed types of pneumococcus can be eliminated the patient's chances of recovery are considerably improved.

(5) There are certain people who are very susceptible to pneumonia and suffer from repeated attacks of the disease. Some of these individuals are infected with different types of pneumococcus in each instance. In other instances the patient is being re-infected with the same type of pneumococcus. In any case, if such patients were vaccinated perhaps once a year with a polyvalent pneumococcus vaccine, it is probable that further attacks could be prevented.

Pneumococcus vaccine is contraindicated in patients with pulmonary tuberculosis and in individuals who are suffering from some acute infection. In the army the claim was made by some that pneumococcus vaccine as well as typhoid vaccine predisposed patients to respiratory infections. No adequate evidence, however, of such a predisposition has been established in the case of either vaccine.

Serum Treatment of Lobar Pneumonia.—The original studies by Cole and his co-workers at the Rockefeller Institute have shown that the treatment of pneumococcus Type I pneumonia with pneumococcus Type I serum has a marked influence on this type of pneumonia and greatly reduces the death-rate. In a series of untreated cases the mortality rate for Type I pneumonia was found to be about 25 per cent., whereas in the serum treated cases the mortality rate was only 7 per cent. Since these studies many other hospitals have used antipneumococcus Type I serum with great success, and favorable results

have also been observed by physicians who have employed the serum in private practice. In spite of these results, however, Type I antipneumococcus serum has not come into such wide popularity as its efficacy would seem to justify. Probably the chief reason for this lies in the difficulty of getting prompt and accurate type determinations on cases of pneumonia. Furthermore, there are many physicians who entertain considerable skepticism as to the value of any kind of serum treatment in pneumonia, and still others actually fear serum treatment because of the danger of anaphylaxis. In a recently published article by Cecil and Blake the effect of Type I antipneumococcus serum on experimental pneumococcus Type I pneumonia has been reported. In these studies it was found that in experimental pneumococcus Type I pneumonia in monkeys the intravenous injection of Type I antipneumococcus serum exercised a specific bactericidal effect, freeing the blood promptly and permanently from pneumococci, shortening the course of the disease, and greatly moderating its virulence. Of 5 monkeys inoculated intratracheally with lethal doses of pneumococcus Type I, all developed pneumonia and all recovered following the administration of Type I antipneumococcus serum. Control monkeys, untreated with serum, died. It was also shown that the earlier the serum was administered, the shorter and less virulent was the pneumonia. When serum was administered late in the disease, the treatment had to be continued over a longer period of time in order to save the monkey's life. Frequent injections were also found to be an important factor in obtaining favorable results. Normal horse-serum was found to have no beneficial effect whatever in experimental pneumococcus Type I pneumonia.

The experiments just referred to corroborate clinical evidence as to the great value of Type I serum. In view of these facts, it is obvious that all cases of pneumococcus Type I pneumonia should have the benefit of serum treatment. In order to administer the serum, however, it is necessary to determine first the type of pneumonia from which the patient is suffering. The determination of pneumococcus types by sputum examina-

tion is laborious and time consuming, but if an examination is started as soon as the diagnosis of pneumonia is made, a report can usually be obtained in eight to twelve hours.

During the two recent influenza epidemics a very small percentage of the pneumonias were of Type I origin. There was some excuse therefore for the failure of physicians to carry out bacteriologic examinations of the sputum in all cases. With a return, however, to more normal conditions, it is probable that the incidence of pneumococcus Type I pneumonia will increase and the necessity for type determination in all cases of lobar pneumonia will become much greater.

Method of Serum Administration.—As soon as the diagnosis of lobar pneumonia has been made, a specimen of sputum should be sent at once to the laboratory for a bacteriologic examination. If difficulty is encountered in obtaining a specimen of sputum, a small amount of saliva should be injected into a mouse, as in many cases enough pneumococci will be present in the mouth secretion to make the diagnosis in this way.

Determination of the type of pneumococcus can sometimes be made at once by performing a precipitin test on the patient's urine. As a rule, however, a positive precipitin reaction is seen only in severe cases. The test is easily carried out by mixing urine in quantities of 0.5 c.c. each with equal amounts of antipneumococcus serum of the different types. In positive cases a flocculent precipitate appears in a few moments. Occasionally a positive blood-culture taken early in the disease will afford a simple method of determining the type of pneumococcus. Lung puncture may be resorted to when it is impossible to make a bacteriologic diagnosis by the methods mentioned.

The proper steps having been taken to determine the type of infection, the physician should proceed at once to determine whether the patient is sensitive to horse-serum. First he is questioned as to previous attacks of asthma and hay-fever and also concerning any previous injections of serum. Regardless of the history, however, a skin test is performed to test for hypersensitiveness to horse-serum. This is most easily done by making a small scratch on the skin of the forearm and then touch-

ing it with a drop of horse-serum. If sensitiveness does exist, an urticarial wheal, surrounded by a zone of erythema, will begin to appear in a few minutes. Patients who are sensitive to horse-serum can be desensitized by small subcutaneous injections of serum at frequent intervals, but I should usually look upon hypersensitiveness as a contraindication for serum treatment.

Occasionally patients are encountered who, though giving a negative skin test, show mild symptoms of anaphylaxis when large doses of serum are given intravenously. For this reason it is customary to inject 0.5 c.c. horse-serum subcutaneously into pneumonia patients as soon as the skin test is completed, even though the skin test is negative, for the purpose of desensitization.

If the case proves to be a pneumococcus Type I pneumonia, serum should be administered at once. Serum may be given undiluted or mixed with an equal part of normal salt solution. Personally, I have never seen any objections to administering the serum in the undiluted form. The simplest method of administration is by gravity. The serum which has been previously heated to body temperature is transferred by means of a sterile pipet from the original container to a glass graduate connected with about 2 feet of rubber tubing. There should be a small glass window near the lower extremity of the tubing for the detection of air-bubbles and the lower end of the tubing should be fitted with a stop-cock and an adapter for a Leur needle. The skin at the bend of the elbow is sterilized with iodin and alcohol and a sterile Luer needle is inserted into the vein. As soon as the blood appears in the needle, the rubber tubing is attached and the serum is allowed to run slowly into the vein. The usual rule is to allow only 10 c.c. to flow in during the first ten minutes. After that the serum can be administered more rapidly.

If the serum is to be administered at all, it should be given in large doses. The first injection should be 90 to 100 c.c. and the following doses should be at least that much, unless there is some reason to the contrary. Cole recommends administration of serum every eight hours, that is, three injections every twenty-

four hours until the temperature has come down to 100° F. and remains there. The points to be emphasized in serum treatment are:

(1) The administration of serum at the earliest possible moment; (2) frequent injections of serum; (3) sufficiently large doses of serum. Failure to achieve favorable results is usually due to violation of some one or more of these rules.

In the summer of 1918 there was a small epidemic of pneumococcus Type I pneumonia among the negro troops at Camp Wheeler, in which the mortality rate, in spite of serum treatment, was surprisingly high. In a series of 29 cases of pneumococcus Type I pneumonia that received Type I serum, there were 10 deaths, a mortality rate of 34.5 per cent. As the mortality rate for Type I pneumonia in cases treated with serum usually varies from 7 to 10 per cent., it was apparent that there was some defect in administering the serum at Camp Wheeler. Investigations showed that two-thirds of the cases treated with serum did not receive their first injection until forty-eight hours or more after admission to the hospital. One-half of the cases did not receive serum until at least four days after admission. The average number of serum injections was three and the total amount of serum given each case averaged about 175 c.c. From these figures it would appear that at Camp Wheeler antipneumococcus serum was not administered early enough, frequently enough, or in sufficiently large doses.

Reaction to Antipneumococcus Serum.—Ordinarily the injection of antipneumococcus serum excites little or no reaction. Sometimes the so-called thermal reaction appears one-half to one hour after the injection. This is characterized by chilly sensations or an actual chill, followed by a rise of 1 to 3 degrees in temperature. This rise is temporary and is followed in turn by a drop in temperature which may be quite extensive. The anaphylactic reaction is a much more serious affair. Symptoms usually appear before the serum injection has been completed, and consist of marked dyspnea, cyanosis, intense anxiety, prostration, and in some cases death. Fortunately this reaction is quite rare and can readily be guarded against by the tests

already described. Symptoms of anaphylaxis can usually be relieved by the hypodermic administration of 10 minims of 1 : 1000 adrenalin solution. The injection of serum should, of course, be stopped with the first signs of an anaphylactic reaction.

Serum sickness is a very common sequel to the serum treatment of pneumonia and usually makes its appearance seven to fourteen days following the administration of serum. The most striking symptom is an urticarial rash which is accompanied by a rise in temperature, general glandular enlargement, and in many cases by pain and swelling in the joints. The condition is often mistaken for a relapse or complication of some kind. The latter can be eliminated by careful physical examination and by the character of the leukocyte count, which in serum disease may be moderately high (15,000–20,000), but with an increase in the relative number of lymphocytes (30–40 per cent.), and frequently with 3 to 7 per cent. eosinophils. Serum sickness usually runs a mild course and should be treated symptomatically.

Discussion.—From this brief review of the serum treatment of Type I pneumonia it will be seen that the procedure is neither difficult nor dangerous if properly carried out. In view of its efficacy in a large percentage of cases there is every reason why the general practitioner should be familiar with the technic in order that he may be in a position to administer the serum when it is indicated. It may be added that most cases of Type I pneumonia are very sick patients and that serum will usually be indicated except in those instances where the type is determined after crisis has occurred.

A word should be said concerning the serum treatment of other types of pneumonia. The workers at the Rockefeller Institute were unable to demonstrate any beneficial results from the serum treatment of Type II and Type III pneumonia. No effort has been made to produce a serum against Type IV pneumonia on account of the large number of varieties encountered. Serum treatment has not been tried extensively in streptococcus pneumonia for the same reason. Several polyvalent antipneumococcus serums have been put on the market,

and such a serum was quite popular in the army. There is no adequate evidence, however, either clinical or experimental, in favor of the polyvalent serum. A polyvalent antipneumococcus chicken serum has recently been highly recommended by Kyes, who reports a greatly reduced death-rate for pneumonias of all types following its use. I have had no personal experience with this serum, so cannot vouch for its value. Finally, it may be said that the treatment of lobar pneumonia is still in many cases a discouraging procedure, but in one group at least, the Type I pneumonias, we have in Type I antipneumococcus serum a therapeutic agent of great power and efficacy.

FROM THE DEPARTMENT OF METABOLISM, VANDERBILT CLINIC, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine. The Application of the Method to Ambulant Patients

By HERMAN O. MOSENTHAL, M. D.

The Neurologic Causes and Effects of Diabetes Mellitus and Their Treatment

By WALTER M. KRAUS, M. D.

The Clinical Determination of Venous and Capillary Pressures

By HENRY ELSNER MARKS, M. D.

The Interpretation of High Blood-pressure Readings

By ERNST P. BOAS, M. D.

CLINIC OF DR. HERMAN O. MOSENTHAL

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RENAL FUNCTION AS MEASURED BY THE ELIMINATION OF FLUIDS, SALT AND NITROGEN, AND THE SPECIFIC GRAVITY OF THE URINE. THE APPLICATION OF THE METHOD TO AMBULANT PATIENTS

For many years it has been generally known that a persistently low urinary specific gravity is a danger signal indicating in many instances a marked degree of renal insufficiency. No effort was made to develop a method which would reveal the degree of urinary concentration that a kidney possessed until Hedinger and Schlayer[1] in 1914 published their work. These clinical investigators showed how, by collecting the urine at two-hour intervals in the daytime and in a single specimen at night, and noting the volume, specific gravity, and the content of salt, much valuable information could be obtained. In carrying out these tests a fixed diet was given for several days.

In 1915 this procedure was somewhat simplified.[2] The American standard of three meals a day was adopted, and only one day of measured diet, covering the period of urine collections, was given. The food of this day contained approximately 13.4 gm. of nitrogen, 8.5 gm. of salt, 1760 c.c. of fluid, and a considerable quantity of purin material in the meat, soup, tea, and coffee. All of these substances have a diuretic action, and it was supposed that the value of the test depended on the mode of excretory response by the kidney to them.

Further investigations, with what has been called the test-meal for renal function, or the two-hour test, showed that some of the original conceptions regarding it were erroneous.[3] It was found that many of the results which were supposedly due

to the action of the diuretic substances, in the prescribed diet, evidently occurred independently of them. The variations in the volume of urine, specific gravity, and concentration of sodium chlorid and nitrogen are somewhat similar whether the diet is that normally taken or is very high or very low in protein content. Furthermore, it was shown that even during starvation, when water only was given at two-hour intervals, in constant quantities, the same variations in volume and specific gravity persisted. It became apparent, therefore, that, with the criteria used for normality, the kind and quality of the food played much less of a rôle than it was consisdered to in 1914.

These observations made it possible to apply this test much more widely than had at first been thought feasible. Much of the labor, principally entailed by the weighing of the food, had been done away with. In the ambulant patient this test presents a peculiar opportunity, since in any individual whose renal function we desire to test we wish to be especially informed concerning the ability of the subject to adjust himself to his usual food and routine life. If a patient can continue his habitual dietary and tasks while the test is in progress, it is obvious that we may then know whether the kidney can handle the customary daily burden imposed upon it in normal fashion or whether it has to put forth an abnormal effort to meet the situation. With such data at hand we are in a position to judge accurately as to whether the existing regimen of the patient is satisfactory, whether greater liberties are permissible, or whether further restrictions are indicated. This has some obvious and distinct advantages over the method, which must necessarily be pursued in hospitals, which standardizes all functional tests and does not adapt them to the patient's requirements and habits.

The following directions are given to our patients:

For.................................... Date..............

DIRECTIONS FOR "TWO-HOUR TEST"

Note time and approximate amounts of food and fluid taken at each meal on the back of this sheet as follows: 8 A. M. Breakfast: 1 orange, 1 dish oatmeal, with cream and sugar, 1 slice of buttered toast, 1 glass of water, etc.

Eat and drink what you are accustomed to, but be sure that *neither food nor drink is taken between meals or after supper until the test is completed.* Any deviation from the directions are to be noted on the back of this sheet.

8.00 A. M. Void urine and discard the urine.
8.00 A. M. Eat breakfast.
10.00 A. M. Void urine and place all in the labeled bottle.
12.00 noon. Void urine and save as before.
1.00 P. M. Eat lunch.
2.00 P. M. Void urine and save as before.
4.00 P. M. Void urine and save as before.
7.00 P. M. Void urine and save as before.
7.00 P. M. Eat supper.
10.00 P. M. Void urine and save as before.
8.00 A. M. Void urine and save as before, adding all urine voided between 10.00 P. M. and 8 A. M.

Send the specimens to the laboratory by 9 A. M.

The above schedule is timed so that it meets the habits of the average person living in New York. It should be revised to meet individual needs, and adjustments can be readily made. There is only one direction that must be insisted upon, that is, that the night urine must be collected at a time beginning three hours after supper and no sooner. If this hour is anticipated a nocturnal polyuria may be simulated because the increased urine volume which usually follows the evening meal would be included with the night specimen. A bag containing compartments for eight 600 c.c. (20 ounce) wide mouthed bottles with etched labels is furnished the patient. This allows one bottle for each of the two-hourly specimens and two bottles for the night urine. The time of voiding is noted upon each bottle when it is removed to collect the urine.

The specific gravity and volume are tested in the usual manner; the chlorids and nitrogen may be determined in the individual specimens, in the total day and night urine, or in the mixed twenty-four-hour amount. Volhardt's method has been used for the estimation of chlorids; the hypobromite determination for urea will yield results that closely approximate the figures obtained by the most accurate methods. The amount of urea, determined by this procedure, divided by the factor 2.14, which reduces the urea to terms of nitrogen, gives good duplicates with

the Kjeldahl method for total nitrogen. This is not generally supposed to be true, but the following table will show that in our hands the hypobromite determination is productive of results that are perfectly adequate from the clinical point of view (Table I):

NITROGEN GM. PER 100 C.C. URINE

Kjeldahl method.	Hypobromite method.
2.04	2.15
2.25	2.34
2.20	2.15
2.15	2.15
1.61	1.36
2.13	2.15
1.76	1.76

Table I.—Comparative values for total nitrogen in the urine by the Kjeldahl and hypobromite methods. The results agree very closely and show that the simple hypobromite method is available for clinical use, if the urea figure is divided by 2.14 to reduce it to terms of nitrogen and the result obtained be considered as representing total nitrogen and not urea nitrogen only.

Case Report.—Mrs. R. J., sixty-one years old. Five years ago an ophthalmologic examination revealed changes that suggested some renal or arterial disturbance. The systolic blood-pressure since that time has varied between 200 and 180 mm. of mercury. For about four years she has become easily fatigued and has fainted at times; there are occasional dizzy spells, and lapses of memory are becoming more frequent; otherwise no indications of cerebral vascular involvement have occurred. The patient complains of dyspnea on exertion and some cardiac palpitation on lying down. She has to void her urine once or twice at night. There are no further complaints or symptoms worthy of note.

Physical Examination.—A rather small, well-nourished female who looks about her age. The skin is somewhat pale and pasty; the mucous membranes and finger-tips are slightly cyanosed; the peripheral arteries (radial, brachial, temporal) are not thickened; the blood-pressure is 220/140; there is a slight pulsation in the suprasternal notch; the heart, although normal

in size, has a distinctly heaving apex impulse and a moderate accentuation of the aortic second sound, which has a slightly ringing quality; the heart sounds are clear and there are no murmurs; the lungs give evidence of a moderate degree of emphysema; the abdomen is negative; the knee-jerks and pupillary reaction to light and accommodation are normal; there is no edema of the ankles nor of the face or back.

Urine.—Specific gravity 1017, faintly acid, a faint trace of albumin, no sugar, and on microscopic examination, very many epithelial cells, an occasional leukocyte, but no casts.

Hemoglobin.—Ninety per cent.

Blood Chemistry:

Glucose	0.12 per cent.
Urea nitrogen	11.20 mg. in 100 c.c.
Creatinin	1.56 " "
Uric acid	5.19 " "

Phenolsulphonephthalein.—Forty-six per cent. excreted in two hours and ten minutes.

TWO-HOUR TEST FOR RENAL FUNCTION

Time.	Volume c.c.	Specific gravity.	NaCl.		Nitrogen.	
			Per cent.	Grams.	Per cent.	Grams.
8–10	174	1007				
10–12	40	1015				
12– 2	22					
2– 4	48	1025				
4– 7	128	1023				
7–10	134	1022				
Total day,	546		.76	4.15	.57	3.1
10– 8	1022	1012	.70	7.15	.28	2.9
Total, 24-hour,	1568			11.30		6.0

The food consumed during the test was noted by the patient as follows:

8.15 A. M. *Breakfast,* 1 glass water, ½ cup coffee, 2 rolls and butter, ½ grapefruit.

1. P. M. *Dinner,* 1 small plate chicken soup, chicken ½ second joint and a piece of breast, 1 tablespoon fresh string beans, 1 tablespoon of rice, 1 dish of fruit sauce, 1 plate of apple sauce, 1 cake, ½ slice bread.

7 P. M. *Supper,* Not quite ½ small lobster, ½ slice bread and butter, 5 lettuce leaves, 1 small plain cake, 3 teaspoonsful of apple sauce.

It is evident that we are dealing with a case of marked increase of blood-pressure. The function of the kidney, as revealed by the blood chemistry, phthalein excretion, and two-hour test for renal function is but very slightly impaired. It is certain, therefore, that there is no marked renal lesion. Consequently, we are justified in the assumption that this is a case of so-called essential hypertension in which the blood-pressure is the factor that has brought about a slight renal arteriosclerosis, some cerebral arteriosclerosis (as evidenced by the fainting spells, vertigo, and poor memory, while the hemoglobin is normal), and a cardiac hypertrophy.

What I wish to discuss particularly in this case is the significance of the two-hour test. Taking up the significant points one by one, and keeping in mind that we wish to determine their value particularly in the ambulant patient, we have:

1. **The Specific Gravity of the Urine.**—(*a*) The *maximal specific gravity* in this case is 1025. In any normal individual this should be 1020 or over. This patient, therefore, exhibits a specific gravity well above the normal, and her power of concentrating the urine is satisfactory and perfectly sufficient to meet her needs.

This high specific gravity in itself is evidence of normality for only a limited, though very essential, part of renal function. This is the ability of the kidney to concentrate. The total renal output for a given period of twenty-four hours depends upon one other factor, namely, the volume of urine which is excreted. The specific gravity in itself, if the amount of urine is high, is an absolute guarantee of normal renal function. There are only two conditions which have a urine with a high specific gravity in which the kidney activity may be impaired. These are passive congestion of the kidney and acute, subacute, or chronic diffuse nephritis. The types of nephritis which may have such a specific gravity are those associated with considerable albuminuria and edema. In them, as well as in passive congestion, there is an oliguria and a very much diminished salt excretion. Both of these deviations from the normal can be readily detected in the twenty-four-hour specimens, and may make the diagnosis clear

in those rare cases in which clinical examination does not reveal the true state of affairs.

With the two-hour test, in normal persons, a specific gravity of about 1020 will be present in one of the specimens regardless of the quality of the diet even during starvation. Since a specific gravity of this height is considered to be such a valuable guide as to the ability of the kidney to functionate properly by concentration, you may well ask why should we take so much trouble to obtain such a specimen with an obligatory high specific gravity? This question is a perfectly proper one, and the answer is one which I trust will aid you somewhat in judging of renal function. In the first place, a casual specimen voided at any time whatsoever if it has a specific gravity of 1020 or over may be considered to be as good an indication of normal renal concentrating power as any sample passed in the course of the two-hour test; however, a persistently low specific gravity in any number of individual specimens is of no significance, but if it exists throughout the seven voidings of the two-hour test we may be certain that the concentrating power of the kidney is lowered.

In the second place, there are no simpler methods of obtaining a sample of concentrated urine. This may seem an exaggerated statement to you. We may gain some knowledge on this point by noting the procedure necessary to force the kidneys to concentrate. Most of us would imagine that if no food or fluid is taken after supper that the first specimen obtained after the night voiding, that is, after an abstinence from fluid of about twelve hours, would necessarily be concentrated. This is frequently not the case even in perfectly normal individuals. Many years ago some German investigators made the observation that there frequently was a polyuria early in the day—uninfluenced by the diet—and that this holds true may be seen from the following examples (Table II):

SPECIFIC GRAVITY OF URINE, LAST TWO FIGURES ONLY

1.	24	25	30	30	32	28	28	28	27
2.	28	28	32	22	23	19	31	15	11
3.	15	19	15	12	26	11	17	09	15
4.	22	15	22	18	28	20			

Table II.—Specific gravity of urinary specimens of normal individuals collected on consecutive mornings. The urine represents the renal excretion from 6 A. M. to 8 A. M. No food or fluid had been taken after supper of the previous day. Many of these specimens have a specific gravity below 1020, thus showing this procedure has no value as a concentration test.

Carrying this procedure one step further and giving a dry breakfast consisting of toast, butter, 1 or 2 eggs, and salt, after the night, during which no food or fluid was taken, the same unsatisfactory results appear. It may be noted from the table how the specimens obtained from 11 A. M. to 1 P. M. sometimes were greater in amount and of a lower specific gravity than those representing the 9 to 11 A. M. hours. This is in all probability due to the diuretic action the salt and protein materials exert even in the absence of an intake of fluid (Table III):

	Time. A. M.	Volume, c.c.	Specific gravity.	Time. P. M. A.M.	Volume, c.c.	Specific gravity.
1........	9 to 11	140	1019	11 to 1	90	1023
2........	"	192	1019	"	60	1026
3........	"	75	1018	"	86	1022
4........	"	98	1024	"	160	1015
5........	"	184	1017	"	130	1019
6........	"	152	1019	"	74	1025
7........	"	108	1019	"	105	1018
8........	"	132	1016	"	66	1023
9........	"	94	1019	"	78	1018

Table III.—The urinary specimens whose volume and specific gravity are shown here were collected after a dry breakfast consisting of toast, butter, eggs, and salt. No food or fluid had been taken since the previous night's supper. It is evident that as a concentration test this procedure is a failure, inasmuch as the specific gravity is frequently below 1020. About 100 such tests were performed—only the results in which either the 9–11 or the 11–1 specimen have a specific gravity below 1020 are detailed in the table.

Other efforts in the same direction have been made. In some German Clinics concentration and dilution tests are carried

out. Examples of these may be taken from Munk's book[4] (Table IV).

NORMAL INDIVIDUAL				CHRONIC NEPHRITIS			
Time.	Urine.		Fluid intake, c.c.	Time.	Urine.		Fluid intake, c.c.
	Volume, c.c.	Specific gravity.			Volume, c.c.	Specific gravity.	
7.30 A. M.			1500	7.30 A. M.			1500
8.00 A. M.	135	1029		8.00 A. M.	185	1009	
8.30 A. M.	100	1013		8.30 A. M.	295	1005	
9.00 A. M.	400	1003		9.00 A. M.	225	1004	
9.30 A. M.	520	1002		9.30 A. M.	260	1003	
10.00 A. M.	285	1004		10.00 A. M.	190	1005	
11.00 A. M.	55	1015		11.00 A. M.	215	1006	
12.00 M.	80	1017		12.00 M.	155	1005	
2.00 P. M.	65	1025		2.00 P. M.	105	1012	
4.00 P. M.	95	1028		4.00 P. M.	170	1016	
6.00 P. M.	110	1023		6.00 P. M.	125	1013	
8.00 P. M.	50	1027		8.00 P. M.	202	1013	
8.00 A. M.	210	1031		8.00 A. M.	335	1016	

Table IV.—Examples of combined dilution and concentration tests as given by Munk.

This method yields results that are as satisfactory, but not more so, than the two-hour test. However, it entails too much discomfort for the patient ever to become a method of choice.

There is a possibility of developing a simple test that will reveal a urine of high specific gravity in those capable of excreting such specimens. A procedure of this sort would probably be of greater value to the general practitioner than any of the tests for renal function thus far devised.

(*b*) *Variation of the Specific Gravity.*—The variation of the specific gravity figures from the highest to the lowest should be 9 degrees or more. In the patient under consideration we see that the highest specific gravity is 1025 and the lowest 1007, the variation of 18 degrees presented may, therefore, be considered to be well within normal limits. In cases of myocardial insufficiency and chronic or acute nephritis with edema, this ability to vary the concentration becomes lost and the specific

gravity is fixed at a level of about 1020. Why the urine does not usually concentrate at higher levels in such patients is a problem which remains to be solved. There are many types of disease in which the urinary specific gravity remains fixed at lower levels—diabetes insipidus, chronic nephritis, marked anemia, the elimination of edema, cystitis, pyelitis, polycystic kidney, prostatic hypertrophy, urethral stricture, paralysis of the bladder (as in tabes dorsalis or tumor of the spinal cord), etc. In all of these instances the power of the kidney to functionate depends upon the compensating polyuria; if this is lacking we are confronted with a very serious condition.

Another aspect has been developed in connection with the fixation of specific gravity which is of considerable importance as a therapeutic guide. Lyle and Sharlit showed that during hot weather, when there was a very great loss of fluid through the skin, a fixation of specific gravity occurred at a high level.[5] This is perfectly true. Others have expressed the opinion that since the surrounding temperature and the activities of the patient have such a far-reaching effect upon the water which may be diverted from the kidneys, it would be best to keep the patient in bed under as nearly constant conditions of rest, temperature, diet, etc., as possible. There is much to be said in favor of this if we desire to test all individuals under exactly comparable circumstances and make classical studies. However, if we wish to correct a habitual faulty intake of water, it is of the greatest value to have this test performed upon individuals who are up and about, eating and drinking their usual meals and performing their routine duties. It is exactly the value of this aspect of the two-hour test that I desire to emphasize during the present hour. Given a high fixed specific gravity, which occurs because an individual is drinking too little water, we may conclude that there is a strain put upon all the organs that require moisture for the performance of their physiologic tasks; the skin becomes dry and is prone to various affections, the mouth is parched, the tongue furred, the bowels constipated, and the bladder and urethra irritated by burning micturition. These symptoms I have observed and have been able to correct when the patient

has been induced to drink more water. What effects an insufficient supply of fluid may have upon gastric secretion, the flow of bile, the blood concentration, the heart-beat, etc., are largely matters of speculation. However, there may be some symptoms resulting from the self-imposed privation of water which many patients, notably women, voluntarily inflict upon themselves. The two-hour test reveals this deficiency when the specific gravity is high and fixed. The therapeutic answer to the problem is self-evident.

A low fixed specific gravity is a danger signal and its cause must be sought. The many possible diagnoses that such a state of affairs would indicate have already been alluded to. Each of these conditions demands therapeutic considerations peculiar to itself.

2. **The Volume of Night Urine.**—An increased volume of urine at night is known as a sign of inability of the kidney to concentrate, and as a compensatory phenomenon by means of which solids can be eliminated under such conditions. It has been established that according to the method of the two-hour test, regardless of the diet, the night urine in a normal person may be as high as 750 c.c.; it is somewhat suspicious of renal insufficiency if it is more than 400 c.c. The quality of the diet may materially influence the degree of polyuria when renal function is impaired; the following table may serve to demonstrate this (Table V):

VOLUME C.C.

NIGHT URINE WITH TWO-HOUR TEST

Case.	Low protein diet.	High protein diet.
1	400	780
2	610	1300
3	595	1910
4	525	1170
5	520	1250
6	507	1004

Table V.—A few examples of patients whose renal function is somewhat impaired. The nocturnal polyuria disappears with a low protein diet when the amount of solid material to be excreted by the kidney is diminished.

Inasmuch as a nocturnal polyuria puts a strain upon the kidney, it is desirable to eliminate it by means of a proper diet. It is evident that the two-hour test carried out on patients who are eating their customary food will inform us as to the presence or absence of an increased night urine under those circumstances, and in that way allow us to judge of whether the diet ought to be curtailed in certain respects or whether it should remain unchanged. The indication of the particular kind of food ingredient that should be adjusted must be obtained from the chemical examination of the blood and urine.

In our case the night urine measures 1022 c.c. This is too high and, if possible, should be lessened. How it may be reduced can be determined when we take up the question of sodium chlorid and nitrogen elimination. What I should like to emphasize at this time is that by carrying out the test in a patient who is pursuing her regular life and diet we know that these are imposing an undue strain upon the kidney and should be remedied. An example of the value of the present procedure is as follows: Mrs. S. carried out the two-hour test while on one of the forced high protein diets commonly in vogue. Her night urine, on this régime, measured 1040 c.c.; a few weeks later, while taking her customary food, the nocturnal polyuria had disappeared and the volume of the night urine was 375 c.c. Obviously in her case the diet need not be changed as far as the nocturnal polyuria is concerned. The two-hour test, in this instance, carried out upon the ambulant patient has given us much more valuable information than the more classical procedure with a set food intake.

3. **The Excretion of Sodium Chlorid.**—The total quantity of chlorids excreted under the present mode of administering the test, that is, while the patient is taking his or her customary diet, enables us to judge of the amount habitually ingested and excreted in the twenty-four hours. In the patient we are now discussing the salt excretion is rather high—11.30 grams. This is probably one of the causes of the nocturnal polyuria. On inquiry as to her habits of using salt, we find that she is indulging in it freely. Her daily output of sodium chlorid should be

reduced to about 5 grams not only to reduce the nocturnal polyuria and relieve the strain upon the kidney but also for the possible effect it may have upon the blood-pressure. By the present method of using the test we have discovered an important error in this patient's dietetic habits which would have escaped us had we used a test diet which would have tried out her powers of eliminating salt.

4. **The Excretion of Nitrogen.**—Much that was said under salt excretion concerning the particular adaptability of the present test as a therapeutic guide holds true as well for the urinary nitrogen. A total of 5 to 6 grams of nitrogen a day is considered as the minimum daily excretion in the urine if we wish to maintain the health and strength of our patients. By means of a high starch, low protein diet this can be accomplished. The above amount of nitrogen represents an intake of approximately 35 to 40 grams of protein. The patient before us has a disease, essential hypertension, in which we wish to furnish a maintenance diet and not exceed it. She excretes 6 grams of nitrogen in her urine during twenty-four hours. Therefore we may consider that her usual protein intake is within reasonable bounds and no further restrictions as to her protein food need to be imposed. The blood uric acid is rather high, 5.19 mg. in 100 c.c. (upper normal limit 3 mg.). This may be associated with an early impairment of renal function or it may be significant of a disturbed uric-acid metabolism, much as we believe it to exist in gouty individuals. In either event it would be indicated to diminish the purin intake. Consequently, our patient has been asked to eliminate the meat soups and gravies from her diet, and to take mostly boiled or steamed meat and fish after the fluid, which has extracted the purin materials, has been poured off. The blood urea nitrogen and creatinin are well within normal limits and no further adjustment of the diet is necessary from any indication they furnish.

It may be worth while summarizing exactly what points are of value to the physician in the two-hour test. The particular feature I wish to call your attention to at the present time is that by allowing the patients to pursue their routine duties and

customary diets we have, in the first place, simplified the test so that it may be readily carried out by the ambulant individual, and, in the second place, have a procedure which gives us a very great amount of information upon which to base exact and rational therapeutic directions. A summary of the criteria of value and their interpretation when the two-hour test is carried out as described, is as follows:

Criterion.	Normal standard.	Significance.
Maximal specific gravity.	1020+	Ability of the kidney to concentrate the urine. If this is as high or higher than the normal standard, renal excretion is satisfactory provided the amount of urine is adequate. This may be regarded as a definite criterion of renal function which is independent of the diet administered. Long life is often possible even if the specific gravity is below normal, provided the inability of the kidney to concentrate is compensated by polyuria, as in diabetes insipidus and a few cases of chronic nephritis.
Fixation specific gravity.	Variation of 9 degrees +.	Normal renal activity is characterized by variation of the specific gravity in the two-hour test. (*a*) A high fixed specific gravity may occur in normal individuals because they take too little fluid to meet their bodily needs. The possibility of determining this makes the two-hour test especially valuable in ambulant patients who are taking their usual amount of food and fluid and pursuing their accustomed occupations. (*b*) A high fixed specific gravity may be brought about by diseases characterized by edema and oliguria, especially myocardial insufficiency and acute or chronic nephritis. (*c*) A low fixed specific gravity is found in many widely varying conditions: diabetes insipidus, chronic nephritis, marked anemia, the elimination of edema, cystitis, pyelitis, polycystic kidney, prostatic hypertrophy, urethral stricture, paralysis of the bladder (as in tabes dorsalis or tumor of the cord), etc. Such patients do well as long as polyuria compensates for the lack of power to concentrate.

Criterion.	Normal standard.	Significance.
Nocturnal polyuria.	750 c.c. or less.	A high night urine means that the kidney is putting forth a greater effort than it normally should. This overstrain may cause fatigue, that is, functional damage, if continued indefinitely. In nephritis, the increased night urine may be reduced by curtailing the food intake. By testing the ambulant patient while on his normal diet we are in a position to judge as to the effect the customary food and habits have upon the volume of night urine and to advise the patient intelligently as to the modification of the diet. The chemical examinations of the urine and blood tell us in what respects the food intake should be changed.
Sodium chlorid excretion.		This is being taken in greater amounts than necessary if more than 5 grams are present in the twenty-four-hour urinary specimen. The amount in the food should be reduced if therapeutic indications demand it. If the amount in the urine is very low and edema exists, then the elimination of salt is insufficient and the amount in the urine cannot be regarded as an index of the quantity in the food.
Nitrogen excretion.		If 5 or 6 grams are eliminated in the urine, there is sufficient protein in the food to maintain an individual's health and strength, provided the diet contains a considerable amount of starch. Unless the disease is of such a nature as to demand the restriction of protein food it is not necessary to limit the protein ration.
		The blood, uric acid, urea, and creatinin indicate whether there has been any retention of these products. These findings must be taken into consideration with the urinary analyses in order to come to a definite conclusion regarding the kind and amount of protein food that is best for the patient in question.

It is obvious that many points which may be utilized for the patient's benefit may be derived from an analysis of the twenty-four-hour specimen for salt and nitrogen, while the customary food is taken, that would be valueless and even misleading with other forms of diet.

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und

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THE NEUROLOGIC CAUSES AND EFFECTS OF DIABETES MELLITUS AND THEIR TREATMENT[1]

A. The Neurologic Causes of Diabetes Mellitus.
B. The Neurologic Effects of Diabetes Mellitus.
- I. Neurologic Conditions Due Primarily to Diabetes Mellitus.
- II. Neurologic Conditions Not Due Primarily to Diabetes Mellitus.
  1. True Multiple Peripheral Neuritis.
  2. Herpes Zoster.
  3. Cerebral Accidents of Vascular Origin.
  4. Arteriosclerotic Conditions Causing Pain.
  5. Vasomotor and Trophic Diseases.
- III. Neurologic Conditions of Doubtful Origin.

C. Treatment.
D. Conclusion.

A. THE NEUROLOGIC CAUSES OF DIABETES MELLITUS

On theoretic grounds it would be expected that it would not be difficult to find diabetes mellitus after certain lesions of the brain, spinal cord, and peripheral nerves. Disease of the pathway from the center of Claude Bernard in the floor of the fourth ventricle to the spinal cord and thence to the adrenals would

[1] A complete review of the literature and the statistics of the 450 records examined at the Metabolic Department of the Vanderbilt Clinic of the New York College of Physicians and Surgeons will be given in a paper to appear later.

I wish to express my thanks to Dr. Herman O. Mosenthal for the privilege of working in the Metabolic Clinic and of reviewing the splendid case reports gathered there during the last ten years.

appear to furnish abundant cause for diabetes. As a matter of fact such an etiology is very rare. Tumors of the medulla associated with permanent diabetes as well as tumors of the cervical cord and vagus nerve have been reported. But these are curiosities. Trauma of the head causes a transitory glycosuria in a considerable number of cases, but permanent glycosuria (diabetes mellitus) is very rare from this cause.

Briefly, therefore, the neurologic causes of diabetes mellitus are of minor importance.

B. THE NEUROLOGIC EFFECTS OF DIABETES MELLITUS

These are of much greater importance. They have been recognized for many years. Herpes zoster was first described by Barbier in 1856; neuralgias, by Worms in 1880. Absence of knee reflexes by Bouchard in 1884. Fischer describes diabetic pseudotabes in 1886, v. Leyden described polyneuritis in 1888, and Leichtentritt and Williams described posterior root and column disease in 1893 and 1894 respectively. Thus these complications are not new to us.

I. **Neurologic Conditions Due Primarily to Diabetes Mellitus.**—The most frequent neurologic sign in diabetes mellitus is increase, absence, or diminution of the deep reflexes of the leg, *i. e.*, the knee and Achilles' jerks. Absence of the deep reflexes of the arm as well as of the superficial reflexes (abdominal and cremasteric) occurs much more rarely. Increase (hyperreflexia) occurs in about 10 per cent. of the cases. Diminution (hyporeflexia) and absence (areflexia) in about 30 per cent. of the cases, as a review of 450 case reports from the Vanderbilt Clinic records shows. The Achilles jerks were absent in 64 per cent. of 37 cases, showing that the Achilles jerks are absent more frequently than the knee-jerks. This has also been maintained by Williamson who has devoted much time to the question. *Therefore in every case of diabetes mellitus the Achilles jerks should be tested as well as the knee-jerks.* The reflexes are not always equally affected (Case No. 1), any combination of normal, diminished, or absent reflexes may be found at the knees and ankles. Nor is the condition of the reflexes always per-

manent. Occasionally they become more normal after a period

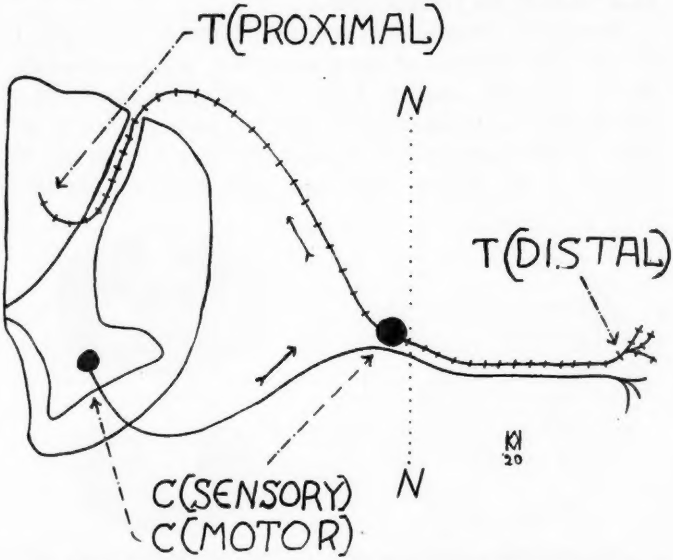

Fig. 34.—Diagram of the parts of a typical sensory and motor peripheral neuron. C, Cell. C (Motor), Motor cell. C (Sensory), Sensory cell. N–N, The line of intervertebral foramina. T (Distal), The peripheral terminals of motor and sensory fibers. T (Proximal), The central terminals of sensory fibers which end in the spinal cord and medulla oblongata. C (Motor) to N, The motor root. C (Sensory) to T (Proximal), The sensory root (radicular portion of the trunk of the peripheral neuron). N to T (Distal), The motor and sensory nerve (neural portion of the trunks of the peripheral neurons).

Disease of the entire peripheral neuron may be called "peripheral neuronitis"; disease of its cell, "cellular peripheral neuronitis"; disease of its trunk or axone, "truncular peripheral neuronitis"; disease of its terminals, "terminal peripheral neuronitis." Up to N the trunk is known as a spinal root; beyond, as a nerve, so that truncular peripheral neuronitis may be divided into radiculitis and neuritis. The roots are partially within, partially without the substance of the spinal cord, so that there may be a further division into intramedullary and extramedullary radiculitis. This may affect either one of the roots, motor (anterior), sensory (posterior), or both. The predominant lesion in diabetes mellitus is an intramedullary posterior radiculitis.

of time. This is relatively infrequent. This hypo- or areflexia may be considered Type B of those neurologic disorders of the

spinal root which result from diabetes mellitus. (See page 235 for a Table of the various types.)

Increase of the reflexes is designated Type A. This may be due to slight irritation of the same nature, which, carried to a greater intensity, leads to hypo- or areflexia. The effect of various factors in causing this sign has been studied in this series of 450 cases, and none have played a part except the severity of the disease. Age, sex, race, nutrition, duration,

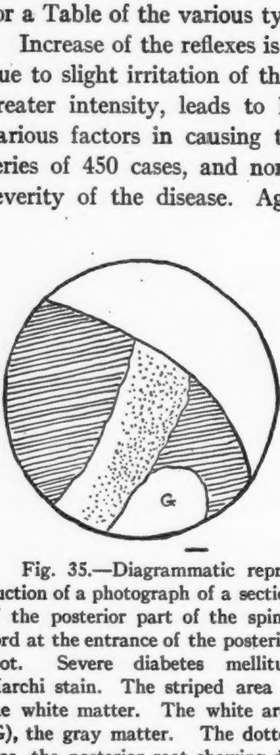

Fig. 35.—Diagrammatic reproduction of a photograph of a section of the posterior part of the spinal cord at the entrance of the posterior root. Severe diabetes mellitus. Marchi stain. The striped area is the white matter. The white area (G), the gray matter. The dotted area, the posterior root showing degeneration. (After Williamson.)

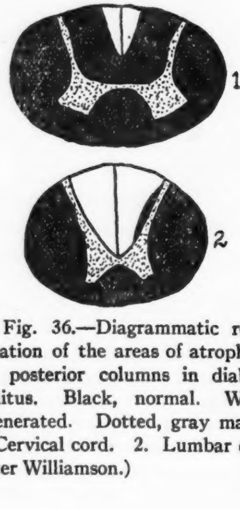

Fig. 36.—Diagrammatic representation of the areas of atrophy in the posterior columns in diabetes mellitus. Black, normal. White, degenerated. Dotted, gray matter. 1. Cervical cord. 2. Lumbar cord. (After Williamson.)

acidosis, blood-pressure, and arterial conditions played no part so far as the statistics show. The cases were classified as severe, moderately severe, and mild. The knee-jerks were absent in 50 per cent. of the severe group, 36 per cent. of the moderately severe group, and but 22 per cent. of the mild group. Thus it appears that, contrary to those factors noted above, *the severity of the case is of importance.*

The pathologic basis for the absence of deep reflexes is a degeneration of part of the intramedullary portion of the posterior

root (Fig. 34). Indeed, there are pathologic reports of such degeneration without any areflexia. The evidence for this is clear cut and sufficient to warrant its acceptance. Williamson, Kalmus, Scheigger, and others have demonstrated this involvement of the intramedullary portion of the posterior roots with resultant degeneration of the central continuations of these fibers in the posterior columns up to the nuclei of Goll and Burdach in the medulla (Figs. 35, 36). It is most conspicuous in the cervical and lumbar enlargements. The degeneration begins just *within* the pia mater.

The next stage clinically resulting from this degeneration is a group of symptoms. This consists of paresthesiæ and partial areflexia (knee-jerks and Achilles' jerks or either). In other words, Type B plus paresthesiæ. This will be called Type C.

Case I.—Dispensary No. 1080. A. R. Female.

The patient is sixty-five years of age. Married.

Chief Complaint.—Polydypsia, polyuria, and weakness.

Present History.—The onset of the disease was in 1915. The patient has been on a moderately restricted diet without ever being sugar free. She has lost 18 pounds and feels weak. She has suffered with pains in the left leg for three months. These are worse at night and occasionally awaken the patient.

Past History.—There is no history pointing to venereal disease. The patient denies the use of alcohol.

Physical Examination.—October 29, 1919: The patient is a poorly nourished woman. The pupils are normal. A systolic murmur at the apex was not well transmitted. The heart was not enlarged. The arteries were not palpable. The blood-pressure was 155/85. There was slight dulness at the apices.

Neurologic Status.—*Cranial Nerves.*—All the cranial nerves were negative.

Sensation.—The sensation was normal throughout, with the exception of tenderness of the calf on the left.

Co-ordination and Movement.—Normal.

Reflexes.—The left knee and Achilles' jerks were absent. All the other reflexes were normal.

November 20, 1919: The reflexes were the same as found in the first examination. There was 0.36 per cent. sugar. Acetone +.

Diagnosis.—Partial unilateral involvement of the intramedullary portion of the lumbar and sacral posterior roots.

Comment.—This case at first gives the impression of a unilateral sciatic neuralgia; however, the absence of the knee-jerk indicates more than sciatic nerve involvement. There is no evidence of neuritis.

The type just described may have another sign and symptom added, dissociated hypo-esthesia or cutaneous sensory changes, involving touch sensation and sparing pain and temperature sensations. This is Type D.

Case II.—Dispensary No. 1216. C. C. Male.

The patient is fifty-two years of age.

Chief Complaint.—General weakness, constipation, and numbness in the hands and feet.

Present Illness.—Sugar was first discovered on February 2, 1920. For four weeks before the sugar was found the patient noticed a feeling of numbness in the extremities and of "pins and needles" in the hands and feet. There were occasional shooting pains in the extremities. The patient has lost 18 pounds since the onset.

Past History.—There is no history of alcohol or of venereal disease.

Physical Examination.—February 9, 1920: The pupils are normal. The cardiovascular system is normal. The blood-pressure 110/80. There are no abnormal pulmonary signs. The abdomen is negative.

Neurologic Status.—*Cranial Nerves.*—Negative.

Co-ordination and Movements.—Normal. There is no ataxia.

Sensation.—There is diminished sensation to cotton wool of "glove and stocking" variety, diminishing to normal at the elbows and knees. There is no change in sensation to pin prick or to heat or cold.

Reflexes.—Biceps, radial, periosteal, and Achilles' jerks not

obtained. The triceps and knee-jerks were present and equal (R = L), but diminished. Nerve trunks not palpable or tender.

Urine.—Sugar, 8 per cent. Acetone +. Diacetic +. Specific gravity 1032. Wassermann negative in the blood.

Diagnosis.—Partial lesion of the intramedullary portion of the posterior roots.

Comment.—This case would give the impression of a multiple neuritis were it not for the absence of weakness and atrophy and of changes in sensations other than light touch.

To all of these may be added signs of disturbance of proprioceptive sense, ataxia, changes in vibration sense, and the sense of position at joints. This is the condition known as **Diabetes pseudotabes.**

Case III.—Dispensary No. 1307. R. A. Male.

The patient is fifty-seven years of age.

Chief Complaint.—Difficulty in walking. Pains in the arms.

Past History.—There is no history of alcoholism. There is a history of syphilis at thirty-six years of age, with sore throat, and iritis two years later.

Present Illness.—Sugar was discovered seven years ago; at the same time the patient noticed a tremor of the arms and some difficulty in walking which has persisted until now. *There is no history of any sphincter disturbances.* The patient has lost 33 pounds. He now has shooting pains in the arms.

Physical Examination.—The patient is a well-nourished man weighing 155 pounds. Blood-pressure is 135/88. The arteries are palpable. The heart is negative.

Neurologic Status.—*Cranial Nerves.*—Negative. The pupils react well to light and accommodation.

Co-ordination and Movements.—There is no paralysis. No atrophy. There is some unsteadiness of gait (ataxia). The finger-nose test is poorly done, both right and left. There is a tremor of both hands. The heel-knee test is poorly done (ataxia). The sense of position is absent in the muscles of both hands. With the eyes shut the patient is quite unable to imitate with

one hand the position of the fingers in the other when this is varied by the examiner.

Sensation.—Vibration sense normal. (For other proprioceptive senses see above.) Temperature, touch, and pain senses are normal.

Reflexes.—Both the knee and the Achilles jerks are absent, otherwise the reflexes are normal throughout.

The examination of the blood and spinal fluid was found negative for syphilis.

Urine.—Sugar +. Acetone, none.

Diagnosis.—A case of diabetes pseudotabes or diabetic ataxia. Intramedullary posterior radiculitis of the cervical (pain, tremor, ataxia) and lumbar (abnormal gait, ataxia, areflexia) segments.

Comment.—The absence of any symptoms indicating anterior horn disease is noteworthy.

A further stage (Case IV) shows changes in temperature and pain sensations in addition to those of touch. This approaches the sensorimotor type of peripheral or multiple neuritis typified by alcoholic neuritis except that the *voluntary muscles are not affected* and the lower extremities are usually affected, while abnormalities of the upper extremities are absent. The symptoms of areflexia, ataxia, and changes in cutaneous sensations are of posterior root origin and not of peripheral origin. No further signs (anterior roots) are present. Pathologic evidence supports this.

Case IV.—Dispensary No. 167. A. A. Male.

The patient is fifty years of age.

Chief Complaint.—Diabetes and pain and numbness in the legs.

Past History.—There is no history of alcohol or venereal disease.

Present Illness.—Two years ago the patient began to have a severe pain radiating downward in the right leg. He also had numbness in it and a feeling of "pins and needles." One year later sugar was discovered in the urine. The patient lost 55

pounds in four years. He now complains of severe pains in both legs radiating from the sacral region to the toes. Tingling and a feeling of "pins and needles" still present. The skin is tender over the legs. Radiating pains in the lower abdomen.

Physical Examination.—The patient is an old looking man, very poorly nourished, and weighing 106 pounds.

Cranial Nerves.—Pupils react to light and accommodation. There is a slight nystagmus to the left.

The *heart* is enlarged to the left. The arteries are palpable. The blood-pressure is 150. The abdomen is negative.

Reflexes.—Knee- and Achilles' jerks are absent. There is no Babinski or clonus. The arm reflexes are normal.

Movement and Co-ordination.—These are negative with the exception of myotonic contractions of the extensors femoris occurring on trying the knee-jerks. These last over one minute before subsiding. There is no atrophy, but some general weakness (emaciation).

Sensation.—Sensations of touch, heat, cold, and pain absent in the feet. This diminished in increasing degree going up to the knee, where sensation was normal.

Urine.—Sugar 3.5 per cent. Acetone +. Diacetic negative.

Diagnosis.—Partial intramedullary posterior radiculitis in the lumbosacral region.

Comment.—The complete absence of local weakness and atrophy is striking and indicates the diagnosis.

A syringomyelic type of dissociation has been reported (absence of pain and temperature sense with the presence of touch sense).

In a few cases changes in the anterior horn cells have been reported. But this is very uncommon. Further, clinical evidence of such involvement is extremely rare. It may be responsible for the facial palsies mentioned below.

The frequency of cases in Type A in the series was 10 per cent.; of Type B, 30 per cent.; of Types C and D, 5 per cent.; of Type E, 0.4 per cent., and of Type F, 0.2 per cent. (1 case). (See page 235 for summary of types.)

The pictures described are not always so complete. One or

another symptom may be absent, so that almost any combination may be found.

Combined with these various manifestations of an *intramedullary posterior radiculitis*, as it may be called, are *neuralgic pains*, Type G. (See Cases I–IV.) These are very frequent in diabetes, over 25 per cent. in our series. These have, in all probability, the same origin as the other symptoms mentioned above. Theoretically this is quite possible, but up to the present there is not adequate pathologic proof. Furthermore, all of these pains are not of the same origin. They are sometimes complained of in the calves due to flat-foot, sometimes due to local arteriosclerosis as well as a number of other diseases of the roots or nerves, all of which causes must be ruled out. Pain may be produced by disease of any part of the trunk of the peripheral sensory neurones. The pain of tabes, of syringomyelia, and of various causes of root irritation may be cited as examples. Neuralgic pains of diabetic origin may occur in the area of distribution of any of the spinal nerves or the trigeminal. In the former they appear most commonly as brachial neuralgias (Case III), crural neuralgias, and sciatic neuralgias (see case reports). The other forms are found as well. In one case at the clinic a bilateral meralgia paresthetica was found in the femoral distribution.

Ulcerations and *gangrene* are uncommon. They have occurred in but 5 cases of the Vanderbilt series, about 0.1 per cent. All cases were over forty-five years of age. These occurred on the toes or on the soles of the foot. The gangrenous area is anesthetic. These conditions must be differentiated as to etiology from ulcerations and gangrene due to syringomyelia, spina bifida, tabes dorsalis, myelitis, and Raynaud's disease. Arterial diseases may play a part in causing the diabetic form, as is emphasized by other observers and by the fact that all the cases occurred in this series in patients over forty or forty-five.

The cause of these might be spinal, radicular, or neural (neuritis). At present the evidence is not conclusive enough to say with certainty, but the great prevalence in other diseases affect-

ing the posterior roots or their spinal trophic centers lead to the theory that these also have their origin in radiculitis.

To now a series of 8 pictures have been described. Thus far a discussion of peripheral neuritis has been omitted, but this will be taken up shortly. For the present we have an *intramedullary radiculitis* forming the basis of a variety of types of neurologic disease. The pathologic evidence for the first 5 is easily available in the references given above, particularly Schweigger, who reviewed the literature up to 1908.

To emphasize these types a brief résumé of each will be given:

Type A. Increased reflexes. Hyperreflexia.

Type B. Diminished or absent reflexes. Hypo- or areflexia.

Type C. Hypo- or areflexia plus paresthesiæ in the extremities, all, two, or only one.

Type D. Type C plus changes in light touch sensation.

Type E. Type C or D plus changes in some of the proprioceptive senses, *i. e.*, muscle and joint sense, diabetic pseudotabes.

Type F. Type D plus changes in pain and temperature sense.

Type G. Neuralgia, which may complicate any of the other types.

Type H. Ulceration and gangrene, which may complicate any of the other types.

The types described may be combined as has been suggested or in other ways. *Almost any combination may exist.* The intoxication is not always such as to cause permanent signs and symptoms. It is like the poison of diphtheria in the sense that the intoxication may not produce permanent results. Treatment helps the condition. The nature of the toxin is not known. Acidosis or the degree of hyperglycemia do not appear to be factors, but the severity of the disease does. What the nature of the substance is remains to be discovered.

The important points to bear in mind are:

1. That diabetes mellitus produces in nervous structures a *partial system disease*, temporary or permanent, involving the

intramedullary part of the posterior roots and their central continuations.

2. That this partial system disease may select, in any combination, the various functional groups of fibers of the posterior roots having to do with touch, temperature, cutaneous or deep pain, proprioceptive senses, or the reflex arc.

This form of neurologic disease is a result of diabetes mellitus and is present in some form in at least 60 per cent. of the cases.

II. Neurologic Conditions Not Due Primarily to Diabetes Mellitus.—1. True **multiple peripheral neuritis** is a rarity in diabetes mellitus. All writers agree about this. If the cases described above are eliminated few cases of neurologic involvement remain. In our series but one instance of typical polyneutitis, *i. e.*, a picture like that of alcoholic neuritis, occurred. The man was also a chronic alcoholic, so that the case must be omitted. Thus in 700 cases *no instance of true sensorimotor polyneuritis with the weakness (or paralysis), atrophy, electric and sensory changes of this syndrome was found.* A complete review of the literature reveals the following remarkable state of affairs: First, the cases described as having neural changes on pathologic examination (11 in all) were none of them of the sensorimotor type. On the other hand, the cases described as "polyneuritis" were none of them well defined as to the *absence* of other causes or the *presence* of the syndrome. Findley's case was tuberculous, with a positive sputum, and died during an attack of fever. Marinesco's and Nonne's cases showed marked degenerations of the anterior horn cells which would naturally cause a descending degeneration in the nerves. Nonne's resembled progressive muscular atrophy rather than polyneuritis. Hartmann and Schrottenback, in Lewandowsky's System, say: "The anatomic basis of neuritic diseases in diabetes has been but little investigated." They are undoubtedly correct. There is no evidence to prove the existence of a true sensorimotor poly*neuritis* due to diabetes. That no such case appeared in over 700 cases at the Vanderbilt Clinic is striking. The matter must be left as follows: 1. There is no pathologic evidence. 2. It is agreed that the occurrence is rare. 3. It is quite possible that polyneuritis may

occur during diabetes, as do other conditions, but other causes for the condition must be sought. It is well known that two poisons acting upon the nervous system may cause a disease which one alone will not. Alcohol is such a cause, and the frequency of this in so-called diabetic polyneuritis has been emphasized by most writers on the subject. The diabetic condition plus another may facilitate the occurrence of polyneuritis, but it does not cause it alone. The importance of this in treatment is obvious. Mononeuritis of the sciatic or its branches, the femoral, obturator, and ulnar are reported. They are rare. The causal relations between these and diabetes must be closly investigated in every instance and the possibility of a radicular origin or a non-diabetic cause must be considered.

2. Another disease which occurs during diabetes is *herpes zoster*. This is unusual and is probably intercurrent rather than causally related.

3. Cerebral accidents of vascular nature causing hemiplegia, etc., must be regarded as due to arteriosclerosis and not diabetes. They are intercurrent conditions, as herpes zoster. Intermittent claudication of the cerebral vessels may occur with transient paralysis.

4. Intermittent claudication of the vessels of the legs (dysbasia angiosclerotica) occurs during diabetes and must be regarded as of vascular origin rather than of diabetic origin. The part which arterial disease may play in causing symptoms of neurologic origin is great. It must be remembered that the age of the patients is most often over forty or fifty. Arterial disease appears to have a definite predisposing influence on gangrene. To what degree it may play a part in the other types is less certain at the present time.

5. Other conditions have been reported, such as Raynaud's and other vasomotor and trophic disorders. These do not appear to be more than intercurrent or concomitant conditions.

III. Neurologic Conditions of Doubtful Origin.—1. Eye palsies may occur. External rectus paralysis and partial third nerve paralysis are rare findings. Argyll-Robertson pupils occasionally are found and may lead to confusion with syphilis.

When diabetes pseudotabes is present the differential diagnosis is more difficult. But the absence of sphincter disturbance and biologic tests indicating syphilis will establish the cause.

2. Facial palsy occurs in a few cases. It is usually transient and may be the first sign of diabetes. The site of the lesion is not known with certainty.

Treatment.—The essential thing is to decrease the severity of the disease by diet. In this way the symptoms may be relieved, particularly the paresthesia, cutaneous sensory changes, and neuralgias. The result may not appear at once. Maintenance of a rigid diet brings improvement in most cases after a while.

Summary.—The neurologic signs and symptoms resultant from diabetes are very common (60 per cent.). They are described in three groups: The first due primarily to diabetes mellitus and resultant from partial system disease involving the intramedullary portion of the posterior roots and their central continuations. Such cases should not be called "neuritis," since this term is a misnomer leading to a misunderstanding of the pathologic basis of the symptoms of the group. The second group is due to causes other than diabetes, but possibly predisposed to by it. The third group is made up of cranial nerve palsies whose primary causal relation to diabetes and pathologic origin remains to be decided.

CLINIC OF DR. HENRY ELSNER MARKS

DEPARTMENT OF METABOLISM, VANDERBILT CLINIC

THE CLINICAL DETERMINATION OF VENOUS AND CAPILLARY PRESSURES

Discussion of the More Important Methods for Determination of Venous and Capillary Pressures. Methods Found Most Accurate and Practical for Clinical Use. Normal Values and Conditions in Which Deviations from Normal are Found.

THE measurement of venous and capillary pressures has been undertaken at intervals during the past by a considerable number of workers using a variety of different methods. For the most part the problem has been taken up as a physiologic investigation, but in a number of instances, more especially in recent years, clinical studies have been made to determine not only normal values but also the nature of pathologic deviations from the normal. Such clinical studies have been made possible by a gradual improvement and simplification in the methods used, but in spite of this improvement the determination of these pressures has remained a task requiring rather too much in the way of apparatus, time, and skill to make it practicable as an ordinary clinical procedure.

The practical application of such determinations has been worked out in only a limited degree as yet. A number of investigators, including in recent years Hooker, Brown, and Clark in this country, have noted the increased venous pressure found with cardiac insufficiency, and Krauss has reported an increase in capillary pressure in this condition, with a decrease in hypertension, nephritis, arteriosclerosis, and diabetes. Variations from normal have been found also in the vascular and vasomotor

disorders, as in the Raynaud syndrome, in thrombo-angiitis obliterans, in ischemic gangrene, and in neurotics and patients with vasomotor instability. In the diagnosis of mechanical venous obstruction the determinations have proved of value, especially when unilateral or localized increase of pressure has been found.

The work undertaken in this clinic has consisted largely in trying out and comparing various methods which have been described for the determination of these pressures, and in devising new methods and modifications of the older ones in the hope of eliminating many of the difficulties and sources of error encountered. It is felt that a discussion of these technical difficulties and a description of the methods finally adopted as most practicable and most reliable may prove of some value to other investigators in this field. To this will be added a brief summary of clinical findings in the series investigated to date.

VENOUS PRESSURE

For the determination of venous pressure compression methods were first used. Following the technic of Hooker,

Fig. 37.—Glass capsules.

Brown, and others, glass capsules of various forms were employed, either covered with a loose rubber membrane, as Brown recommends, or sealed directly to the skin, according to the technic of Hooker, and then connected to a water manometer and inflating bulb. The ones found best adapted to the latter method are shown in Fig. 37, A and B. These are respectively 15 and 20 mm. in diameter.

As recommended by Hooker, the capsules were at first sealed to the skin with collodion. This, however, is a tedious and time-consuming process, an air-tight seal is secured with difficulty,

and when secured it is usually frail and incapable of retaining as high a pressure as one often desires to use. Various other adhesives were tried before a satisfactory one was found. As now used, this consists of Burgundy pitch melted with about one-fourth its quantity of inspissated Canada balsam and allowed to cool. Such a mixture becomes soft and highly adhesive a little above body temperature. In using, the glass capsule is warmed and its edge rubbed across the surface of the pitch. A film of the melted pitch adheres to the glass. In order to avoid excessive heat the operator should test the temperature of

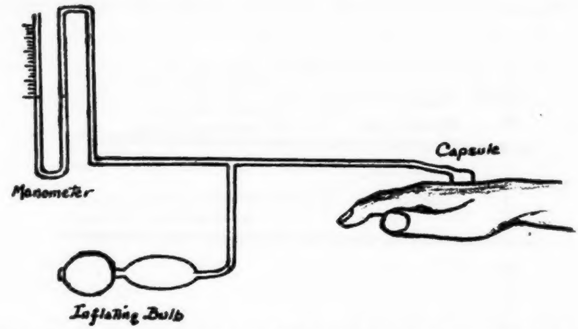

Fig. 38.—Diagram of apparatus for determination of venous and capillary pressures by compression method. For reading maximum capillary pressures a single-tube water manometer, with reservoir at the lower end, was connected in the circuit, for convenience in measuring the higher pressures. (After Hooker.)

the glass carefully against his own skin before applying the capsule to the patient. The capsule is now placed upon the spot selected and pressed down for a few seconds, when it will adhere firmly. A moist or greasy skin may require cleaning with alcohol and ether before the capsule is applied.

For inflating the capsule a cautery bulb may be used with the air bag about half-filled. By compressing the latter with the hand a rapid and delicate control of pressure may be maintained.

The subsequent technic varies. Hooker and others vary the pressure in the capsule while noting the point at which the vein

collapses, and the point at which, being collapsed, it again becomes visible when the pressure is reduced. Brown collapses the vein in the capsule, then strips the vein proximally from the capsule as far as a valve, or keeps it compressed with the finger, then gradually reduces the pressure in the capsule until the stripped portion fills. Neither of these methods has proved to be entirely satisfactory. The collapse of a superficial vein does not occur suddenly when the external pressure reaches a certain point, but progresses gradually as the pressure is increased. The degree of distention of a vein is then a point of equilibrium between a number of factors. The forces which tend to distend the vein are internal pressure and the resistance of the wall and

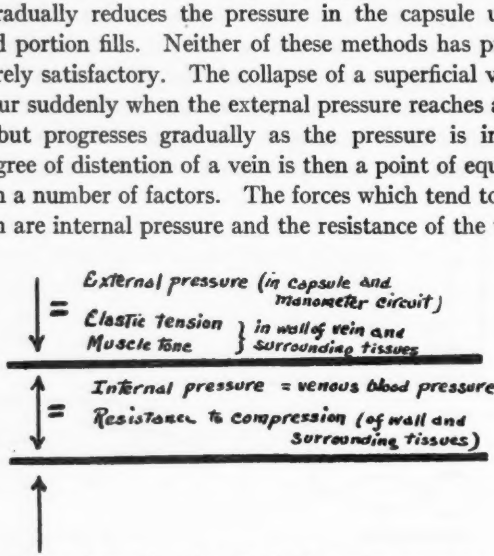

Fig. 39.—Factors influencing size of vein in venous pressure readings by compression methods.

surrounding tissues to compression; those which tend to reduce its size are the external pressure, the elastic tension of the vessel wall and surrounding tissues, and the tone of the muscle-fibers in the vein. When external pressure is increased the sum of the latter factors becomes greater than the sum of the former, and the degree of distention decreases. Now, however, the elastic tension of the vessel wall and tissues has a smaller value, since they are stretched less, and when this decrease balances the increased value of external pressure a new point of equilibrium is reached, the vein having a smaller diameter than at the lower external pressure. This gradual decrease in diameter takes place through a considerable pressure range before complete collapse occurs.

The actual point of complete collapse is exceedingly difficult to determine even in the most superficial and prominent veins; moreover, this point cannot be assumed to represent the true internal pressure, regardless of the other factors mentioned. Tissue resistance itself may account for a considerable portion of the external pressure used. Further, unless the collateral venous circulation distal to the capsule be free, the occlusion of the vein itself may be sufficient to cause an increase of pressure distal to the capsule.

When the capsule is inflated the resultant force on the skin to which it is sealed tends to cause that area to assume a spheric form or, rather, that of a segment of a sphere. The forces now tending to compress the vein are not only the hydrostatic pressure of the fluid column of the manometer normal to the surface, but another element also normal to the surface, due to the stretching

Fig. 40.—Distortion of skin produced by inflation of capsule sealed to it. Pressure in capsule must not only compress the vein, but must also overcome tension of stretched skin.

of the skin horizontally, where it rises over the vein. Subtracted from the sum of these two factors is a third element normal to the surface, but negative in sign, that due to the elastic tension of the spheric segment of skin. Without determining the magnitude of these forces we are scarcely justified in assuming that the pressure in the capsule when the vein collapses coincides with the pressure inside the vein.

The method of Gärtner was used in a few cases. In this method a prominent superficial vein of the hand or forearm is observed while the part is raised and lowered, the height at which collapse occurs being noted in its relation to the heart level. Here again only subjects with prominent veins are suitable, and the difficulty in reading the point of complete collapse is no less than when the capsule is used.

In order to avoid the inherent error of the above methods

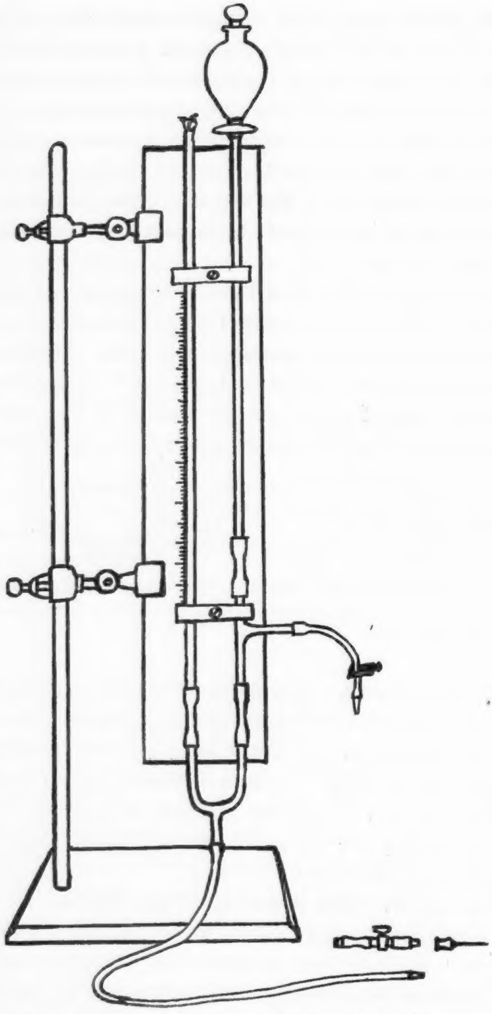

Fig. 41.—Apparatus for intravenous determination of venous pressure. (Modified from Moritz and von Tabora.)

the direct intravenous method described by Moritz and von Tabora was tried. In this method a hollow cannula or intra-

venous needle is introduced directly into the vein. The needle is connected with a fluid-column manometer, with the fluid at a height well above the pressure to be expected in the vein. Upon opening the stop-cock the fluid drops until the hydrostatic pressure of the column equals the pressure in the vein. No blood should enter the cannula, the flow being always into the vein. The manometer is filled with sterile physiologic saline solution and the glass and rubber parts are easily detached for sterilization in the autoclave.

The apparatus shown in Fig. 41 consists of a vertical glass manometer tube, mounted over a millimeter scale, to which is connected by a Y-tube a parallel vertical tube with a reservoir at the upper end. To the latter tube a side tube with stop-cock is attached for convenience in lowering the fluid level in the manometer. A long rubber tube with a pinch-cock leads from the stem of the Y to a stop-cock provided with Luer connections at each end.

In using this apparatus it is first necessary to establish a zero point on the scale. Moritz and von Tabora showed that in the recumbent position the orifice of the right auricle lies 5 cm. below the anterior surface of the chest wall at the level of the fourth rib, or 1 to 2 cm. lower when there is pigeon-chest deformity of an excessive amount of subcutaneous fat. To determine this level a square is used which has a long arm about 50 cm. in length and a short arm of 5 cm. The long arm carries a spirit level. With the patient recumbent and his shoulders horizontal, the square is placed transversely on the chest at the level of the fourth rib, the end of the shorter arm is brought against the skin of the axilla, and a mark made at the point of contact, this mark then being 5 cm. vertically below the anterior surface of the chest wall. The manometer is placed on a table beside the patient and the long arm of the square is used as a straight-edge and level to find the point on the manometer scale which lies at the same level as the mark on the skin. This point is then at the same level as the orifice of the auricle and is the zero point.

The patient's arm should be free from clothing and should

be abducted at a right angle and supported so that there is no pressure upon it.

A small glass syringe is now half-filled with the sterile saline solution and connected to the stop-cock section and needle. Venipuncture is performed, the stop-cock opened, a few drops of blood withdrawn into the syringe to make sure of the needle's position in the vein, and the needle at once washed by injecting the saline and blood into the vein, at the same time releasing the tourniquet. The stop-cock is now closed, the syringe removed and replaced by the manometer tube, the pinch-cock being released when the connection is made. Upon opening the stop-cock the manometer column will drop, at first rapidly, then more slowly, showing the respiratory waves of venous pressure, and, during expiration, cardiac waves also. The fluid soon comes to rest except for the respiratory fluctuations, usually about 1 mm. in height. In many patients larger fluctuations also occur, with an amplitude of several millimeters, or sometimes of more than a centimeter, and with an irregular period—usually about forty seconds.

To repeat the reading, the stop-cock on the reservoir is opened enough to permit the manometer column to rise a few centimeters and the fluid is again permitted to flow into the vein.

If care is taken to prevent a reverse flow—as may happen on coughing, on forced expiration, or during the fluctuations referred to—the needle will remain patent.

The long rubber tube, stop-cock section, needle, and syringe are sterilized for each determination; the rest of the apparatus is autoclaved at frequent intervals.

A small correction of the reading should be made for capillary attraction in the manometer tube. With a tube of 3 or 4 mm. internal diameter this usually amounts to from 3 to 5 mm.

Venous pressure readings obtained with this apparatus are found to be considerably lower than the values found with the compression methods. To date a series of 23 patients has been studied by this method. When the vein was close to zero level all normals showed venous pressures between 4 and 6 cm. Normal values reported by workers using compression methods

have usually been given as from 5 to 15 cm. Patients with cardiac insufficiency show an increased pressure. The only other case in which an increased pressure was found was a young man

Compression Methods		Direct Puncture	
Clark	Briscoe	Moritz and von Tabora	Elpers
5 - 15 cm.	men 9-12 cm women 7-11	1.0 - 9.0 cm. most subjects. 4.0-8.0 Av. 5.2	2.1 - 12.0 cm. most subjects. 5.0-8.0 Av. 6.6

Table 1.—Normal venous pressure values as reported by various authors.

with a well-marked "irritaple heart," vasomotor instability, and an arterial pressure of 146/68, whose venous pressure at zero level was 7.3 cm., a little above the run of normals.

Case No. 1162		Case No. 982	
Vein Level	Venous Pressure	Vein Level	Venous Pressure
-5.2 cm	5.5 cm. 5.6	-6.1 cm.	9.8 cm 7.7 9.8 7.5 6.5 5.9
+0.2	5.95 5.95	+0.2	4.1 4.1 5.3
-16.8	4.2 4.3	- 6.3	5.9 4.9

Table 2.—Case No. 1162, showing normal agreement of successive readings, compared with case No. 982, a neurotic and apprehensive patient, in whom readings show wide fluctuations during observation.

Neurotic patients in general show a marked lability of pressure, with wide fluctuations during observation and a tendency often to show subnormal pressures—one woman having a pressure of 1.7 cm. with the vein 2 cm. below the zero level.

In general, as the vein is depressed below the zero level there is a slight fall in pressure or, rather, the pressure does not increase as much as would be expected if the hydrostatic column were to be added to the pressure at zero level.

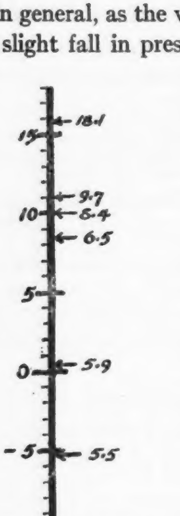

Fig. 42.—Patient No. 1162. A typical case, showing the progressive fall in venous pressure as the part is lowered with relation to the heart level. Intravenous method. Left, vein level in centimeter above and below zero level. Right, venous pressure in centimeter water.

CAPILLARY PRESSURE

As with venous pressure, there are two general methods for the determination of capillary pressure; compression methods, in which color changes are observed as pressure is applied to the skin, and direct puncture methods. In addition, Lombard has observed, under the microscope, the actual collapse of the capillaries under pressure, the skin having been made transparent with glycerin. This method, however, is scarcely adapted to clinical work.

The results reported by Krauss, working with both puncture and compression methods, together with the great superiority of the direct method in the measurement of venous pressure, led us to experiment with the puncture methods used by Krauss and with various modifications, in the hope of finding a method at once accurate and of clinical usefulness. The technic finally adopted is as follows:

The apparatus consists of a short, light glass tube (about 30 x 5 mm.) having a flat, out-turned flange at one end. The other end fits, not too tightly, into a rubber tube which forms one branch of a Y, the other branch running to a vertical glass manometer tube, with a millimeter scale, and the stem connecting with a 30-c.c. glass syringe, filled with saturated sodium

bicarbonate solution. The hand is supported on a stand, and the tube is supported vertically just below the tip of a finger in such a way that when sealed to the finger it will exert practically no pressure or pull on the skin (preferably on a balanced arm).

The tip of the finger is cleaned and dried with ether and alcohol; the horny layers of the skin are then carefully shaved from a small area with a razor blade. The glass tube is now warmed at the flame and the flange rubbed over the pitch mixture. A superficial puncture wound is now quickly made in the shaved area and the tube at once applied and held for a moment until it adheres firmly, then filled with the sodium bicarbonate solution, the finger turned palm downward, and the tube inverted over the end of the rubber tube, which is filled with the same solution. The end of the glass tube is now carefully introduced into the rubber tube, care being taken to avoid breaking the seal and to prevent air-bubbles from entering. A light should be arranged just behind the glass tube.

If the puncture has been properly performed a fine thread of blood will be seen to issue from the wound and drop in a straight line from it. Pressure on the plunger of the syringe now causes the manometer column to rise. As the pressure increases the flow is decreased, and finally stops, but may reappear when the pressure is lowered, if the wound is sufficiently deep.

With good illumination the flow is easily observed. There are, however, practical difficulties encountered in using this method which make it extremely unreliable, chiefly the impossibility of making uniform punctures. The wide variations in the readings obtained serve to indicate the variability in depth and extent of the punctures. In many trials we have seldom found it possible to obtain duplicates on the same patient. If the puncture be shallow, bleeding will often stop before a satisfactory reading can be obtained, and will not start again, while a deeper puncture will continue to bleed against the highest pressures that can be employed with the apparatus—40 cm. or more. Such discordant results have led us to abandon the method, though Krauss states that he was able to make readings which checked well with the figures obtained by his compression

method. He mentions, however, that when the readings were high he could not be sure that they were not due to too deep a puncture.

Fig. 43.—Spring tonometer for measurement of capillary pressure.

Many varieties of compression methods have been used by different investigators, and with wide variations in the results reported. Von Recklinghausen used thin rubber bags with openings at top and bottom, the upper opening being covered with glass. Lombard used chambers having a top of glass and covered at the bottom by a loose membrane of transparent gold-beaters' skin. The finger having been adjusted in position beneath the chamber, the pressure inside the chamber was increased until a color change was noted. Krauss used this method in conjunction with the puncture method of Basler, and his own modification of the latter, comparing them on the same patients. Hooker and others have used the glass capsule, sealed to the skin with collodion, as for determining venous pressure, and I have found this method, with the pitch seal, most convenient and satisfactory. A water manometer is used and, for inflating, the cautery bulb and air bag, by which rapid changes and delicate control of pressure can be secured.

I have also used a spring tonometer, as shown in Fig. 43. This consists of a brass tube, a spiral tension spring (wound from No. 0 or 00 silvered music wire), and a light glass rod carrying at its upper end a scale, marked on a paper tube. The tonometer is calibrated in grams on a pair of balances, the scale being read against the upper end of the brass tube. Care should be taken to hold the tonometer vertically both in calibrat-

ing and in making observations. A glass disk 11.3 mm. in diameter (this giving it an area of 1 sq. cm.) is placed on the skin area selected and the tonometer is used to apply pressure, the stylus being held perpendicularly against the center of the disk. Good illumination is necessary, and if the skin is well saturated with glycerin before the disk is applied the color is more easily observed. The scale reads directly in grams pressure per square centimeter of surface. This instrument is particularly useful for determining pressures on the mucous membrane of the lip—a region in which color changes are easily read and the error due to tissue resistance is at a minimum, but where it is not practicable to seal the capsule.

In using this method on the skin the application of pressure to the disk causes a deformity of the tissues as shown. As a result of this deformity the tissues are not compressed uniformly, but in decreasing proportion from the periphery to the center.

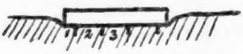

Fig. 44.—Unequal distribution of pressure under disk, resulting from tissue deformity when pressure is applied.

In the peripheral zone (zone 1) the pressure is greater than the average pressure per unit of surface, and this zone shows the greatest blanching, while the central zone (zone 3) always shows the least blanching. Between the central and peripheral zones is a zone (zone 2) where the pressure is equivalent to the average pressure per square centimeter shown on the scale, and the color change in this zone corresponds fairly closely to the changes obtained with the capsule method. The method, however, is not as satisfactory as the capsule method, and the readings obtained are usually noticeably higher than with the latter.

With all compression methods the color change is a gradual one, with a wide range of pressure change between the first observable paling of the skin and complete blanching. As Lombard has shown by microscopic observation of the cutaneous vessels under pressure, this is due to a progressive diminution in caliber as the pressure is increased plus a progressive obliter-

ation, the various portions of the capillaries—from deep plexus through papillary loops to superficial plexus—collapsing at different pressures according to their position in relation to the arterial or venous end of the capillary network. A variety of criteria have been employed by different investigators in establishing values for capillary pressures. Hooker, Briscoe, and others have recorded as the capillary pressure the point of complete blanching. Other investigators have used, in turn, the point at which color returns after blanching, the point at which the first observable fading of color could be noted, and the point at which the first distinct blanching took place. In all these cases the personal factor of the observer introduces a large element of error, for a difference in pressure of several centimeters may cause only a slight change in tint of the skin. The result of this lack of uniformity in criteria is shown in the values given for normals by different investigators. These range from 6 to 12 cm. at the lowest to 70 to 90 cm. at the highest—discrepancies due no doubt to differences in methods of applying pressure as well as to differences in criteria.

The explanation of these discordant results lies in the fact that investigators have sought to establish a fixed and definite value for capillary pressure, when, as has been indicated, different portions of the capillaries collapse under different pressures, and it is probable also that a color change may be observed even before any of the vessels are completely collapsed. Under such conditions it is obviously impossible to apply pressure over a considerable area and assume that some particular point in the color scale represents a definite "capillary pressure." There is no "capillary pressure" except as we speak of the pressure at a particular point in the capillary system. We may, however, by establishing an arbitrary color criterion compare capillary pressures in different patients, without regard to the question of the actual state of collapse of the various sections of the capillaries, or the absolute value of the intracapillary pressure. In the earlier part of our work I took as such a criterion the first observable blanching of the skin as pressure was increased. Later I found more information to be gained by taking two values,

the first observable blanching, and the pressure at which complete blanching ensues, or, better, the pressure being alternately

Compression Methods.	Direct Puncture	
Briscoe	Bosler method	Krauss.
Men 20-26 cm Women 19-27 cm.	8.0-12.0 cm.	Men. 8.0-11.0 Women. 7.0-10.5

Table 3.—Normal capillary pressure values as reported by various authors.

increased and decreased, the point at which color comes and goes with a slight decrease or increase of pressure.

In many cases as the pressure was increased to obtain complete blanching a marked capillary pulse became visible, and in such cases both systolic and diastolic values were determined when this was possible. Usually, however, it was impossible to measure systolic pressure, as the manometer used provided a fluid column of only 80 cm. length, while considerably greater pressure was often necessary to blanch the skin in systole.

In order to obtain uniform and comparable readings it is necessary always to use the same illumination in observing the color changes. I have found it most satisfactory to use a nitrogen (daylight) Mazda lamp, mounted on a bracket, directly over the capsule, the upper half of the lamp being shielded with a metal-foil sheath. This light, I think, is somewhat superior to daylight for observing color changes in the skin.

No attempt will be made in this place to draw definite conclusions as to normal and abnormal capillary pressures and their relation to the various conditions present in the patients studied. The series studied so far, by satisfactory technic, comprising 41 observations on 27 patients, is far too small to permit of any generalizations being made on the basis of these observations, and as the values obtained are at variance with some of those reported by former investigators it is felt that a considerably larger series will have to be studied before definite conclusions can be formed.

We feel, however, that the investigation to date has been successful in establishing a practical and satisfactory technic for the determination of capillary pressure, and, furthermore, that the practice of reading both maximum and minimum values, and when a capillary pulse is present the systolic and diastolic values as well, has great advantages over making a single reading at an arbitrarily chosen point. These two points are more easily established than any point of intermediary color change, and are less subject to error arising from the personal factor. Moreover, the double reading provides not only an approximation of the absolute height of pressure at the two ends of the capillary system, but indicates the magnitude of the total fall in pressure between the two ends as well. While it is still to be proved that

the values obtained coincide with the actual intracapillary pressures, this is less important than the fact that the method does give values which are comparable in different patients and which may be used as a measure of the actual pressures.

Thus, 14 observations on 9 normal subjects so far have given minimum values of from 5 to 8 cm. of water. (Other observations on supposedly normal subjects indicate that the normal minimum may be as high as 12 cm.) Maximum values have varied from 23 to 37 cm., and normals so far observed have not shown marked capillary pulsation; 5 of 7 cases of arterial hypertension so far studied have shown marked capillary pulses, with systolic pressures of over 50 cm. The diastolic pressure in general appears to be higher when the arterial diastolic pressure is high. Observations were usually made on the palm of the hand.

One patient with diabetes, arteriosclerosis, and healed gangrenous ulcers of the foot showed a marked erythema of the toes and distal third of the dorsum of the foot when the foot was dependent. This was associated with considerable pain and discomfort, which, with the congestion, was relieved by elevating the extremity. Capillary pressure measurements in this patient showed an enormously increased pressure when the foot hung down or the patient was in the erect position. Upon elevating the foot the capillary pressure fell, and when the foot was 15 to 20 cm. above the heart level it blanched completely and the capillary pressure could not be read. This is in contrast to the normal, in whom the effect of hydrostatic pressure at different levels is more or less completely compensated for, and in whom, while the capillary pressure shows slight changes with change in level, we find neither congestion of dependent parts nor blanching of elevated ones.

The measurement of systolic capillary pressures in hypertension has not as yet been satisfactorily carried out because of the difficulty in obtaining a seal that will withstand the high pressures. Up to about 80 cm. of water the pitch seal is satisfactory, but with higher pressures it usually gives way. Normals may show a capillary pulse with a systolic pressure above 80

cm., but the pulse has not been found to be as marked in appearance or the diastolic pressure as high as in hypertension. While Krauss reported a lowered capillary pressure in diabetes, arteriosclerosis, nephritis, and hypertension, we have not confirmed this in the cases studied.

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THE INTERPRETATION OF HIGH BLOOD-PRESSURE READINGS

The Variability of Blood-pressure in Normals; in Neurocirculatory Asthenia; in Hypotension; in Hypertension. The Effects of Exercise on Blood-pressure. Treatment of Hypertension.

UNTIL quite recently the blood-pressure, as measured in millimeters of mercury by means of the sphygmomanometer, has been regarded as a static phenomenon. If a patient's pressure has been, for instance, 150 systolic and 100 diastolic, we have considered these figures a fixed measurement of the blood-pressure, just as we regard a hypertrophied heart as an enlarged organ of definite size, constant for the time being, until further pathologic change takes place. But we are gradually realizing that such an interpretation of the blood-pressure is incorrect, that in reality the variations in pressure are very great, the readings inconstant, and difficult to evaluate. It is with these facts in mind that I wish to present several different types of cases, all of them illustrating the variability of blood-pressure readings, and the care that must be taken in their proper interpretation.

The literature of the last ten years on blood-pressure is very extensive, and contains frequent notes on the variation of the pressure under different conditions, such as exercise, meals, and intercurrent diseases, such as the gastric crises of tabes, of lead-poisoning, and so forth. But apparently there has been no gen-

eral appreciation of the fact that any isolated blood-pressure reading is without meaning unless the conditions under which it was taken have been standardized. This has rendered valueless most of the therapeutic studies on hypertension, for, as we shall see, results which would be considered wonderful therapeutic successes can be reproduced by proper attention to the conditions under which the blood-pressure estimations are made. Tixier in France[1] and O'Hare[2] and Mosenthal[3] in this country have clearly shown the importance of these normal variations.

The first patient whom I shall present is a man thirty years of age, who feels perfectly well, who has never had any severe illness, and appears for examination just to make sure that he is in good health. Careful examination from head to foot reveals no signs of disease. His blood-pressure readings, taken while he is recumbent, are as follows:

Time.	Blood-pressure.	Pulse.
On lying down	136/84	76
After seven minutes	120/80	80
After sixteen minutes	118/80	84

Thus, we see at the very outset that a single reading is deceptive, and is not an accurate measure of the true pressure. You will notice that there was no significant change in the pulse-rate during the observations, and that the man was not at all excited or disturbed by the procedure.

As a further illustration of the same phenomenon let me cite the case of a soldier, a candidate for the aviation service, whom I examined as cardiovascular examiner for an aviation examining board. He was a strapping, well-developed young man, twenty years of age, in apparently perfect condition. He had been painstakingly examined by a group of specialists, and no departures from the normal had been found. Subsequent to the cardiovascular examination he was subjected to the Bárány tests, and no defects in equilibration were discovered. His heart was normal and he reacted well to exercise. Yet the blood-pressure readings, at first glance, were far too high. The measurements were taken with the candidate in the recumbent posture:

Time.	Blood-pressure.	Pulse.
On reclining	150/85	100
After five minutes	150/85	100
After ten minutes	146/85	96
After fifteen minutes	145/80	96
After thirty minutes	140/80	92

It was evident that the man was excited, and that until he calmed down no normal readings would be obtained. So he was assured that he would pass the examination, but would have to have another test of his blood-pressure. At the second examination he was not nearly so nervous, he knew what was going to be done to him. The blood-pressure, taken in the same manner as on the day before, now read as follows:

Time.	Blood-pressure.	Pulse.
On reclining	140/85	96
After five minutes	140/85	92
After fifteen minutes	134/80	84
After twenty-five minutes	128/80	80
After thirty-five minutes	125/80	80

This clinical picture was not unique among the aviation candidates who were examined; in fact, it was far from uncommon. How then are we to interpret such findings, and which of the readings are we to choose as the normal? If we take such repeated blood-pressures on a large series of individuals, we find that in almost every instance the initial readings are higher than the subsequent ones. Finally, we arrive at a stage at which the figures remain constant. Tixier has called this the *residual blood-pressure,* and it is probably the most accurate measure of the tension that we can obtain. What the cause of these variations is will be considered later.

The same variability shows itself in the blood-pressure of patients with hypotension. We find it in tuberculosis, as well as in certain low tensions associated with internal secretory disorders. The initial reading will be relatively high, only to fall in from fifteen to thirty minutes. Thus, in such a case the initial reading may be, for instance, 120/70, giving no hint of a hypotension. But if we make repeated observations we may

find that within twenty minutes it drops to 105/70, revealing the true condition. As an illustration I shall present the chart of a tuberculous patient, a young girl nineteen years of age, with advanced bilateral tuberculous infiltration and cavitation of the lungs, whose temperature ranges from 99° F. in the morning to 103° F. in the afternoon. She is a rather nervous girl. She was in bed when the blood-pressure was taken and had not been up for the preceding twelve hours.

Time.	Blood-pressure.	Pulse.
First reading	128/76	116
After eight minutes	110/76	124
After seventeen minutes	110/76	116
After twenty-two minutes	110/80	112

On another day two reading taken fifteen minutes apart were 105/70 and 104/70. Thus her "residual pressure" was between 104 and 110, a fact which would have escaped us if we had relied on the very first figure without further confirmation.

This phenomenon is not so striking in bed patients as in those who are up and about, for the reason that the former are in a more monotonous and quiet environment, and engage in less physical activity than the latter. In other words, the factors which tend to elevate the blood-pressure are not so numerous or so active in bed patients, so that their readings represent more closely the residual pressure.

What are these factors that cause such variations in blood-pressure? Roughly we may say that the level of pressure is determined by the quantity of blood expelled from the left ventricle with each systole, by the frequency of the heart-beat, by the elasticity of the arterial wall, and by the peripheral resistance. These elements may undergo all kinds of permutations and combinations, and at present we have no means of unraveling their relative importance in each particular instance. At times we may venture a fairly accurate guess. We recognize certain vascular crises, such as those associated with the gastric crises of tabes, or with lead-colic, in which there is an acute hypertension, which may be relieved by the exhibition of nitrites. In such instances we are probably justified in attributing the

rise in pressure to a peripheral vasoconstriction. But consider the rise in blood-pressure conditioned by such an ordinary experience as slight exercise or mental unrest. How are we to evaluate that? The factors here are probably chiefly an increase in the volume per unit time output of blood from the heart, achieved by a larger output with each systole, as well as a more rapid heart-rate. But on closer study we find that the pulse-rate, under such circumstances, may vary very little, while the pressure becomes elevated. Are we then to attribute this higher pressure solely to an increased volume output with each systole, or is a vasoconstriction an added element in the change? Furthermore, we must distinguish between the systolic and diastolic pressures. The former is much more variable than the latter, probably because it depends more on the quantity of blood thrown into the aorta with each systole, and this, in turn, hinges on the amount of blood flowing into the heart from the great veins. The diastolic pressure depends more on the maintenance of the peripheral resistance and on the elasticity of the arteries. A more detailed discussion of the problems involved in the proper evaluation of blood-pressure changes is out of place in this presentation. Until new graphic methods are invented that will enable us to answer some of these questions in the particular patient whom we are examining, the explanation of many of the phenomena that we observe must be withheld.

Certain empiric facts, however, are established. We know that exercise usually induces a rise in blood-pressure, and that after meals there is an elevation of about 10 mm. Emotions, pain, and excitement may act similarly. So it is evident that, although we do not understand the real mechanism in these reactions, the blood-pressure in normal individuals undergoes constant variations. In addition to these more patent factors that alter the blood-pressure from time to time there are many subtle influences which escape closer analysis, which are always active, and probably account for the phenomena reported above, and for some that we shall discuss shortly.

One of the most striking instances of unstable blood-pressure is found in the symptom-complex of the "irritable heart of sol-

diers," also known as neurocirculatory asthenia. Of course, these cases are not confined to soldiers, but from the nature of the disorder the symptoms are much more accentuated in soldiers than in the usual run of civilians. The reason for this is that an anxiety neurosis plays such an important part in the development of the symptoms which are thus rendered acute in war time. The disease occurs usually in individuals with a constitutional nervous instability, in whom mental unrest, combined with severe physical exertion, or at times an acute infection, provokes symptoms referred to the cardiovascular system. Chief among these are: precordial pain, palpitation, dyspnea on exertion, vertigo, fainting, tachycardia, and acrocyanosis. The following case is typical:

A soldier, aged thirty, was admitted to the hospital for observation. His family history was negative for tuberculosis or nervous disorders. Past history unimportant. As long as he can remember the patient has suffered from dyspnea, palpitation, and precordial pain on exertion. These symptoms have rarely been acute, because he has always spared himself, and has avoided hard work. Since he has been in the army he has been unable to favor himself in this manner, and consequently the symptoms have interfered a good deal with his activities. He is unable to do double time, and in addition to the former complaints he now has vertigo and headache after exercise, and is unable to keep up with the other men in his company. His hands and feet are often cold. Physical examination reveals no organic defects. Exercise is borne poorly, dyspnea and exhaustion preventing any sustained effort. The pulse is greatly accelerated by exercise, and remains rapid, between 116 and 128, for ten minutes afterward. Blood-pressure readings taken on different occasions show striking variations. They are represented in the following table:

Blood-pressure.	Pulse.
134/90	60
140/80	96
150/86	80
180/95	128

The first of these figures probably approaches most closely his residual pressure. The other estimations were made under varying conditions of excitement and physical activity, and show an exaggerated influence of these factors in the readings. If we had measured the pressure while he was asleep, or after he had been kept tranquilly in bed for twenty-four hours, the reading would undoubtedly have been in the neighborhood of 120 systolic. You will note that the systolic pressure fluctuates much more than the diastolic, and that there is no definite relationship between the pulse-rate and the height of the pressure.

This man has no hypertension. His diastolic pressure is within the range of normal, and his systolic pressure drops to a similar level if we take it at a time when the external stimuli are at a minimum. In other words, the patient has a very unstable cardiovascular system, and shows exaggerated reactions to influences which act similarly, but to a less degree on normal individuals.

Instead of presenting more cases of this type, I shall show a chart with blood-pressure findings of many such patients to show the extreme variability which we may encounter. In each of the patients on whom these estimations were made another measurement taken under favorable circumstances gave a normal reading.

Blood-pressure.	Pulse.
150/90	76
128/70	84
135/90	84
178/60	92
144/80	96
168/85	96
150/85	80
155/90	116
160/90	104
170/90	108
152/90	116
168/85	96
148/76	100
150/80	56
148/80	76

Into quite a different group fall those patients with real hypertension. In them the upward dislocation of the blood-

pressure is persistent, and the diastolic pressure shares in the elevation. Moreover, secondary organic pathologic changes, such as hypertrophy of the heart, with subsequent myocardial insufficiency, arteriosclerosis, and apoplexy, invariably appear sooner or later. If we bear in mind these additional features, the constant increase in diastolic as well as systolic pressure, as well as the secondary organic changes in the cardiovascular system, we shall find no difficulty in differentiating this important group from the foregoing transient and less significant forms of hypertension. I shall show you a few of this type of cases, with chief emphasis on the blood-pressure, so that we may determine whether or not the variability of the sphygmomanometric readings is as great here as in those that have already been discussed.

Case 1034, female, age fifty, married.

The family history is unimportant save for the death of two sisters from pulmonary tuberculosis. The patient has had one miscarriage and one child which died at the age of four months. The menopause occurred four years ago. She has taken four glasses of beer and one of gin until one year ago. The only acute illness which she has had is pneumonia, which occurred thirty years ago during an influenza epidemic. Ever since then she has had periods of great languor, during which she is very nervous and weak, and is unable to sleep. Even between such attacks she is nervous and excitable, at which times she has shakiness and tremor of the hands.

The present illness commenced seven years ago, with dyspnea on exertion. Two years later slight edema of the legs set in whenever she walked much. Gradually these symptoms increased, and, in addition, palpitation and precordial pain became manifest. She now voids four times during the night.

Physical examination shows an obese woman, weighing 186 pounds, with rather heavy features, and thick skin. The tonsils are small, and all but two of her teeth have been extracted. The thyroid isthmus is palpable. The heart is enlarged, measuring 6 cm. to the left of the midsternal line in the second space, and 11.5 cm. in the sixth space. The right border is 3.5 cm. to the right in the second space. The heart-sounds are good,

there are no murmurs, but the aortic second sound is distinctly accentuated. The lungs are clear, and the abdomen, although lax and pendulous, shows no further abnormalitis. The eye-grounds are normal. The urine has a specific gravity that ranges between 1014 and 1020, and is acid. Traces of glucose have been found twice in seven examinations, and a trace of albumin once. Phenolsulphonephthalein output 60 per cent. in two hours. Blood urea nitrogen 14.98 mg. per 100 c.c., creatinin 1.36 mg., and blood sugar 0.107 per cent. The blood-pressure was taken with the patient recumbent on a hard examining table in the dispensary. The room was by no means quiet. The readings on two different occasions were:

	Blood-pressure.	Pulse.
On lying down	176/98	60
After twenty minutes	176/90	60
After twenty-eight minutes	166/88	64
After forty-five minutes	142/82	68
On lying down	158/94	72
After five minutes	155/94	64
After ten minutes	150/90	64
After fifteen minutes	152/90	72
After twenty minutes	148/88	72
After thirty minutes	146/88	64

Case 1129, female, age fifty-four, married.

This patient's history is essentially the same as the foregoing one. The menopause occurred two years ago, and was followed for a year and a half by flushes and choking sensations. The symptoms of the present illness date back three years, when her feet first became swollen. Since then she has developed in addition dyspnea on exertion, substernal pain, radiating to the right shoulder and back, and nocturia. She complains of nervousness, fatiguability, and cold hands and feet. Physical examination again shows an obese woman weighting 179 pounds, with good color, marked dermographia, and hirsutes of the upper lip. The thyroid isthmus is somewhat enlarged, there is cardiac hypertrophy, with accentuation of the aortic second sound, and a systolic murmur at the aortic area. The lungs show a moderate

emphysema, and the liver extends from the fourth intercostal space to 2 cm. below the costal margin. The urine is absolutely normal. Phthalein output 65 per cent. in two hours; blood urea nitrogen 14 mgm.; creatinin 3 mgm.; and blood-sugar 0.149 per cent. Blood-pressure readings taken under the same conditions as in the preceding case:

Time.	Blood-pressure.	Pulse.
On lying down	215/120	72
After nineteen minutes	205/108	80
After thirty-five minutes	210/115	72
After forty-five minutes	198/110	72
After fifty-seven minutes	192/110	72
After sixty-seven minutes	180/105	68
After ninety minutes	176/115	72

Case 1010, negress, age thirty-five, married.

Mother had a left hemiplegia. The patient has had two miscarriages and one baby, which died at the age of one month. No infectious disease except frequent sore throats, which ceased ten years ago. In 1916, while sewing on a machine, and while in a hurry to complete a piece of work, she suddenly became dizzy and experienced palpitation. Since then she has been short winded and has had palpitation on exertion. A doctor having told her that the symptoms were due to a fatty heart, she has been much frightened ever since. From her childhood days she has been, as she says, a coward, and easily perturbed, on which occasions she would feel shaky, and have tremor of the hands. She weighed 158 pounds ten years ago when she was married. Five years later she weighed 170, and today she tips the scales at 183. In 1917 she was told that she had high blood-pressure. Her chief complaints are headache, occasional vertigo, dyspnea and palpitation on exertion, at times slight

On of the legs, and nervousness.

edema physical examination we find little of note. The heart is not enlarged, but the first sound is weak, and the aortic second sound is accentuated. There is a systolic murmur at the apex, transmitted to the axilla, and another systolic murmur at the aortic area. There is marked throbbing of the carotid arteries.

She excretes 57 per cent. of phthalein in two hours, and the urea nitrogen of the blood is 16.4 mgm. per 100 c.c. The urine is normal. Blood-pressure, reclining:

Time.	Blood-pressure.	Pulse.
After five minutes	170/104	116
After ten minutes	165/105	112
After twenty minutes	145/98	92
After twenty-five minutes	152/100	92
After thirty minutes	144/98	100
After forty minutes	140/98	96

Case 1017, male, age sixty-five.

The family history is unimportant. He has taken little alcohol, but drinks four glasses of tea a day. The only illnesses that he has had are typhus at the age of eight, and at fifty-seven an attack of pain in the lumbar region, associated with painful, burning micturition. His doctor told him at the time that he had gravel.

The onset of the present illness was ten months ago, and was characterized by swelling of the feet, followed by swelling of the face and body. With this there was dyspnea on exertion, sleep was poor, and headache annoying. Since then he has voided five times during the day and twice at night. Weight five months ago 233 pounds; present weight 190.

On examination, we find an obese man of rather large frame, and quite senile. No signs of disease are present in any of his organs except in his heart and arteries. The apex is 15 cm. from the midline, in the sixth space, the right border extends 9 cm. to the right of the midsternal line. The apex-beat is diffuse and forceful. The first sound has a poor muscular quality, the aortic second sound is distinctly accentuated and there are no murmurs. The pulse is full and has a quick up-and-down stroke, and shows occasional extrasystoles. The eyegrounds are normal, the arteries not sclerosed.

The urine on several examinations shows a specific gravity between 1013 and 1023, contains no sugar, but gives a four plus reaction for albumin. Microscopic examination reveals a few granular casts and red blood-cells. The two-hour phthalein

excretion is only 22 per cent., the urea nitrogen of the blood is 20.3 mgm. per 100 c.c., and the blood-sugar 0.22 per cent.

Blood-pressure readings:

Time.	Blood-pressure.	Pulse.
On lying down	200/96	88
After six minutes	190/90	88
After twenty-five minutes	170/84	76
After thirty-two minutes	170/90	84
After forty-seven minutes	172/90	72

Time.	Blood-pressure.	Pulse.
On lying down	200/108	84
After seven minutes	190/100	80
After twelve minutes	188/100	80
After eighteen minutes	188/98	80

From the examination of these patients you see that they fall clearly into two groups: the first three, essential hypertension with normal kidney function; the fourth, chronic nephritis with hypertension. In passing it is worth noting that the first group is encountered much more frequently than the second one in an out-patient department. We are gradually learning to appreciate the fact that high blood-pressure does not necessarily mean nephritis. Of course this has been known for many years, and was emphasized by T. Janeway among others in his clinical studies. What chiefly interests us now, however, is the variability of the blood-pressure in both of these conditions. For convenience of study let us tabulate the changes in the pressure in these 4 cases:

Case.	Drop in mm. Hg. Systolic.	Drop in mm. Hg. Diastolic.	Drop in pulse-rate.	Time in minutes.
1034	30	6	20	40
1129a	34	16	+8	45
1129b	12	6	8	30
1010	39	5	0	90
1017a	28	6	16	47
1017b	12	10	4	18

Here are systolic pressures ranging from 170 to 215, dropping as much as 39 mm. within about forty-five minutes, under no other influence than rest, on a hard examining table in a noisy clinic. With this, the diastolic pressure falls to a much less degree. Although the pulse tends to slow at the same time, its rate does

not parallel the change in pressure. Reference to the table will show that in Case 1034 the pulse drops 20 beats, while the pressure falls 30 mm. In Case 1129a the pulse accelerates 8 beats, while the pressure drops 34 mm. Other discrepancies of a similar nature appear on closer study of the chart. But the significant feature is that even after the fall in pressure, the residual pressure, which is analogous to the residual pressure of normal patients described above, still is higher than normal, and more particularly, the diastolic reading remains distinctly elevated. This study shows, then, that in hypertension, just as in the types of cases that we have examined before, the blood-pressure is not a static phenomenon, but admits of wide variations. However, after these fluctuations have been eliminated the residual tension is still too high. This applies both to essential and to nephritic hypertension. O'Hare has reported the same findings quite recently. The importance which the recognition of these facts has on the interpretation of the results of our therapeutic efforts is self-evident, and will be taken up in more detail a little later.

A word as to the technic of blood-pressure estimations will not be amiss. All of these determinations were made by the auscultatory method. It is essential to have the cuff adjusted carefully. Then palpate the brachial artery just below the cuff, and place the stethoscope directly over the vessel. If this is not done, you will miss the first beats indicating the systolic pressure, in cases in which these sounds are not very loud. Be sure to inflate the cuff to a point beyond the systolic pressure, otherwise you may mistake the third phase for the first phase, and so get too low a reading. The determination of the diastolic pressure usually offers more difficulty than that of the systolic. It should be read at the moment when the sharp thump of the third phase changes to the dull thud of the fourth phase. It is well always to double check the auscultatory readings by watching the oscillation of the manometer, and by palpating the radial artery. As a rule, the mercury column begins to oscillate about 10 mm. before the first sound is heard. The pulse is felt coming through at the wrist about 10 mm. below the level of appearance

of the first sound. At times these relationships are reversed, and the palpatory method gives higher readings than the auscultatory one. That is an added reason for employing both methods in every instance. Kilgore[4] in an interesting paper pointed out the importance of the personal factor in blood-pressure measurements by the auscultatory method. Using a stethoscope with two sets of ear-pieces, so that two observers could listen to the sounds during the release of the air from the same cuff, he found that the difference in the systolic readings of the two observers might reach 12 mm., and the diastolic 15 mm. Finally, in noting a blood-pressure reading, it is always essential to state whether the patient was standing, sitting, or lying, whether or not he was excited, whether he had just been exercising, and so forth. Unless all of these factors are known, for they all affect the level of pressure, a single reading is of little value.

Having thus reviewed the variations of blood-pressure as encountered in our every-day routine, let us consider in more detail the effect of exercise upon it. It has long been known that exercise is followed by an elevation of the systolic pressure. It is worth while to examine more minutely the changes that occur. They have been well summarized by Cotton, Rapport, and Lewis.[5] They found that a reading taken from three to ten seconds after moderate exertion is not greatly above the normal resting pressure. From this point the level of systolic pressure rises steeply, and in from twenty to sixty seconds reaches a maximum, from which it falls away gradually to normal in from one to four and a half minutes from the end of the exercise. The probable explanation of this event is that during the exercise the blood is driven from the veins to the arteries, thus depleting the venous reservoirs of the abdomen and of the limbs. "This transference of blood to the arterial system produces with other factors, such as the increased rate and power of heart action, and increased tone of the arterial wall, a high systolic blood-pressure. Immediately at the end of exercise the subject sits and rests, the muscles relax, the depleted veins take up the blood flowing out from the capillaries; the heart is momentarily robbed of its supply; a steep fall of arterial pressure occurs, and the pressure

remains reduced until the veins fill and overflow. This overflow, by feeding the heart, produces the rise of arterial pressure described." Barringer[6] has devoted some study to the effect of exercise on the blood-pressure, and has found similar curves. He finds that the peak of the rise in pressure occurs within thirty seconds after the exercise in normal individuals if the effort does not demand more than 5600 foot pounds of work in sixty seconds. In those with cardiac decompensation, or with a lessened reserve power of the heart, the maximum elevation is delayed until sixty seconds after such exercise. The same reaction occurs in normals in whom the exercise is excessive. There is thus a delay in the rise of the systolic blood-pressure. These observations lend emphasis to the importance of noting, in all studies of the blood-pressure after exercise, the time after the exercise at which the readings are made. Otherwise the recorded readings will not represent the maximum rise in pressure, but may be on either the ascending or descending limbs of the curve. Most of the reported studies of the effects of exertion on the blood-pressure fail to take this fact into consideration. Lowsley[7] studied the effect of exercise on the blood-pressure of young athletes. He found a rise in both systolic and diastolic pressures, greater in the former, followed by a fall below normal which was more marked after the exhaustive types of physical activity. The return to normal often took over an hour. Others have made similar observations on the fall of pressure after exhaustive exercises. Reference may be had to the papers of Albu,[8] Barach,[9] and Potter.[10]

The amount of rise in pressure depends on the severity of the exercise. With a rapid exercise of moderate intensity, normal controls will show a rise in the systolic pressure of from 30 to 40 mm. of mercury. There is little change in the diastolic pressure, although it may rise or fall a few degrees. Lowsley, using the Erlanger sphygmomanometer, found an average rise of 20.3 mm. in the diastolic pressure, but this has not been the universal experience, and is probably to be attributed to the difficulty of reading the diastolic pressure with this instrument. It will be interesting to compare with these figures those which I have

obtained in patients with neurocirculatory asthenia and with hypertension. A general idea of the blood-pressure reaction will best be obtained by reference to the accompanying table of averages:

Diagnosis.	Number of cases.	Initial systolic blood-pressure.	Rise in systolic blood-pressure.	Initial diastolic blood-pressure.	Drop in diastolic blood-pressure.	Return of systolic blood-pressure to old level (minutes).	Initial pulse-rate.	Rise in pulse-rate.
Normal........	?	?	36	?	+20.3	?	?	33.5
N. C. A........	55	138.6	27	82.9	7.2	3.5	87.7	54.3
Hypertension...	21	174.5	30	103.0	1.4	8.6	79.7	14.0

In this table the normal figures are those of Lowsley. The exercise in the patients with neurocirculatory asthenia consisted of hopping on one foot 100 times in about forty-five seconds. The hypertension cases squatted 30 times in forty-five seconds, both exercises requiring the expenditure of approximately the same number of foot pounds of work. You will note that irrespective of the original blood-pressure, and of the health of the patient, the rise in systolic pressure is about the same in all three classes of individuals. This means that the circulation is compensated at its respective level in each type of case for that amount of work. In my two series there was little change in the diastolic pressure. The variance of Lowsley's figures have already been commented upon. In normals and in those with neurocirculatory asthenia, the return of the pressure to its original level is rapid, while in hypertension cases it is a little delayed. The increase in pulse-rate is quite independent of the change in blood-pressure, as is shown in the last column of the table.

While such averages as are given in this table are of some interest, too much emphasis cannot be placed on them, for in a large measure each case, normal or pathologic, is a law unto itself, and no generalization will allow us to predict the reaction in any particular instance. In the hypertensive class it will depend in part on the condition of the heart. A comparison

of the exercise reaction in a selected group of patients with neurocirculatory asthenia and with hypertension, in whom the initial systolic pressure is 160 or above is of interest. I have records of 9 of the former and 15 of the latter. The average systolic pressure of those with neurocirculatory asthenia is 166.6 mm., and the average rise in pressure after exercise is 15.1 mm. The average pressure of the hypertension group is 189.2, and their average rise in pressure after the same degree of exercise is 30.7 mm. The patients with hypertension, in spite of a higher original pressure, show a greater response to exercise, a rise which is about normal. The high initial pressure in those with neurocirculatory asthenia represents the reaction of a hypersensitive vasomotor system to stimuli, which, in a normal individual, have no effect. The influences which have raised the initial pressure act in the same way as does exercise, so that, when the stimulus of exercise is superadded, the factor in the elevation of pressure, which is due to the exercise is small, because, at a given moment, the circulation is capable of only a certain response to a given effort. The true capacity of the patient to respond to effort would be measured by the sum of the elevation of the original pressure above normal, and the added elevation due to the exercise. In this series this average sum is 56.6 mm., which shows a higher range of response than the normal. With this, it is interesting to note that after such exercise the patients with neurocirculatory asthenia show much more dyspnea than normals or than those with hypertension. From these data we may conclude that in patients with hypertension the circulation is carried on at a higher plane of pressure, but that at this level the reaction to exercise within certain limits is essentially normal. Patients with neurocirculatory asthenia, if subjected to exercise at a time when their pressure is at a high level, react to a less degree, because the factors which cause this temporary abnormal elevation are the same as those which are concerned in the exercise reaction, so that, so to speak, the exercise just heightens a reaction which is already taking place.

There is another aspect of the reaction to exercise in the hypertensive group which is worthy of note, and which has a

more practical bearing. That is, that the pressure reaches the pre-exercise level on the average within eight minutes following the exercise, and that in a certain number of instances it falls to a point that is lower than the pre-exercise pressure. The following protocols illustrate this type of response. The patient laid down immediately after the exercise.

Case 1046: Mild diabetes mellitus, obesity, hypertension, enlarged heart.

Time.	Blood-pressure.	Pulse.
On lying down	170/95	80
After ten minutes	170/94	76
After nineteen minutes	160/94	76
Exercise—30 squats in forty-five seconds.		
After 0.5 minute	178/88	88
After 2.5 minutes	160/80	88
After 4.5 minutes	146/84	88
After 6.5 minutes	136/76	80
After 11.5 minutes	132/78	84
After 16.5 minutes	138/80	84

Case 1030: Diabetes mellitus, hypertension, slightly enlarged heart.

Time.	Blood-pressure.	Pulse.
On lying down	220/110	84
After eleven minutes	204/120	84
After sixteen minutes	196/120	92
After twenty-two minutes	220/120	88
Exercise—30 squats in forty-five seconds.		
After one minute	250/116	100
After three minutes	220/112	100
After five minutes	194/112	96
After eleven minutes	194/120	100

Case 1129: Obesity, hypertension, enlarged heart, emphysema.

Time.	Blood-pressure.	Pulse.
On lying down	222/110	80
Exercise—30 squats in forty-five seconds.		
After 0.75 minute	235/110	?
After 1.5 minutes	250/105	108
After three minutes	220/105	96
After four minutes	204/105	92
After eight minutes	184/98	72
After thirteen minutes	184/98	84

In these cases, as in the others, the rise in pressure after the exercise is transient, but, what is more, there is a rapid drop to a level lower than that of the original pressure. Although some of the patients suffer from a moderate degree of dyspnea immediately after the exercise, this does not last long, and there is no sense of exhaustion. The diastolic pressure shares with the systolic pressure in this fall, but to a less degree. It is difficult to explain this lowered pressure after effort. In my opinion, it is not the same phenomenon as the low tension that we see following exhausting exercises. A large factor, I believe, is the decreased systolic output of the heart due to an accumulation of blood in the splanchnic reservoir; although the fall in diastolic pressure suggests that the dilatation of the peripheral arterioles plays a part as well. For the present we must be content with the recognition of the phenomenon, its exact explanation still eludes us.

The treatment of hypertensive states forms a timeworn subject, so that I shall not attempt to consider it systematically. A few points which are suggested by the foregoing discussion are worthy of consideration. The most important one is accurate diagnosis, the recognition of the fact that not every pressure over 120 means hypertensive disease, but that the range of normal pressures is so great that under certain circumstances healthy individuals may present such figures. We must separate those patients with very labile vasomotor systems from the real hypertensive group, and remember that the diastolic pressure is the best criterion of a pathologic elevation of the arterial pressure. In other words, be sure that the patient has hypertension before you treat him for it. Repeated, and at times serial, blood-pressure readings are necessary to establish this point. Second, it is essential to determine whether or not a nephritis accompanies the hypertension. Kidney functional tests are necessary to determine this. Slight albuminuria alone does not always mean nephritis. Remember that the majority of ambulant patients with hypertension have no accompanying renal involvement, but belong to the class of the so-called essential hypertension.

Having determined that the blood-pressure elevation has a real significance, we may consider in what way it will harm the patient. The vast majority of individuals with essential hypertension die from myocardial insufficiency or from apoplexy. It has been claimed that many develop a contracted kidney, secondary to the blood-pressure change, but while this may occur at times, in the majority of cases one of the two other complications will carry off the patient before the kidney disease has time to produce its deleterious effects. In those in whom the hypertension is associated with a chronic nephritis the customary treatment for the latter may be given in addition to the measures that are employed against the high pressure itself.

The fact that death usually depends on secondary disease of the heart or arteries suggests that the cardiovascular apparatus is under a constant abnormal strain from the high tension, and that although it can adjust itself to this increased work for a time, sooner or later it will give out. Our therapeutic efforts, then, until we have fathomed the real underlying cause of the disease, must be directed to the lightening of this strain to the best of our ability. The dictates of common sense and the rules of general hygiene will be our best guides.

Temperance in eating, in drinking, and in smoking will be of greater value than any one particular diet. It has never been proved that a low protein diet or any special diet will reduce the blood-pressure. At times we may have to prescribe a carefully arranged diet for our patients, because nothing else will satisfy them, and because in no other way can we get their co-operation. To tell a patient to be moderate in his eating is far less dramatic than to tell him to eschew red meats and the like. But we should realize that in prescribing a fixed diet we are but striving for temperance in eating, and that the prohibition of certain food-stuffs is not a cure-all. Many patients with high pressure are very obese. In these, a diet that will insure a generous reduction in weight is of real value. For this purpose there is nothing so efficacious as a strict antidiabetic regimen, that is, one in which the intake of fats and carbohydrates is reduced to a minimum. Once the weight has been brought to

an approximately normal figure, the diet should be just adequate to maintain this weight. If the patient complains of hunger on such a diet, he should be taught to "Fletcherize" his food, that is, to chew very slowly and painstakingly. In this manner a relatively small volume of food will satisfy, more than a larger volume hastily consumed.

While on the subject of diets we must keep in mind the recent work of Allen[11] on the value of a diet in which the salt and fluid intake has been reduced to the minimum. He has submitted only a preliminary report of his work, and it needs further study and confirmation. If one can really obtain such reductions in pressure as he has in some of his cases, without weakening the patient too greatly by the extreme deprivation of salt and water, this method of treatment may prove of value. For the present we must regard it as still an open question.

The chief factors responsible for temporary elevations in blood-pressure are psychic or mental disturbances, that is, worry, excitement, great mental activity, as well as all sorts of physical exertion. Both of these must be taken into consideration if we are to attempt to keep the pressure at its lowest possible level. As regards the former, we must study the patient's individual needs and problems. It is not at all advisable or necessary for a man to give up his business and devote the rest of his life to watching the height of his blood-pressure. Again temperance and equanimity are the goals for which we must strive. This point is well brought out in Moschcowitz's[12] recent paper. We must teach our patient to lead an even-tempered and equable life. This is difficult enough in a man of means; but how much more so in a laboring man.

The question of exercise has not been given sufficient attention. That any extremes of exertion are contraindicated is self-evident. We must teach our patients not to hurry, to avoid sudden spurts of speed, such as running up stairs or chasing a street car. But a modicum of well-planned exercise is not only harmless, but is beneficial. The average man or woman in comfortable circumstances, when they reach middle age, the age at which hypertension becomes manifest, lead far too seden-

tary lives. The indications for moderate exercise apply to all, whether the blood-pressure is elevated or not. Tennis or any violently competitive sport is, of course, out of the question. But there are two forms of out-door activity which are ideally suited to this condition. They are walking and golf. The degree of exercise will depend on the particular conditions of the case and the condition of the heart muscle. The best check on the amount of exercise that will be borne is the sense of fatigue and dyspnea which the patient himself experiences. Exercise should always be carried to a point a bit below the threshold of fatigue or dyspnea. Some patients, in whom the hypertension has not yet been followed by organic disease of the cardiovascular apparatus, will stand a greater degree of exertion. Experience shows that many people with hypertension feel better for exercise even when it is fairly strenuous. The explanation for this may lie in the frequent drop in pressure after exercise which was described above.

A more difficult problem is the proper planning of treatment in poorer patients who are unable to limit their physical activity at will. This applies to the mother who must do the scrubbing and cleaning for a large family, and climb, maybe, many stairs of a tenement several times a day; as well as to the father whose work may overtax his capacity. Adequate care of such individuals requires the aid of social service agencies to make the necessary adjustments in the mode of living, and to provide, if necessary, a new and more suitable occupation.

Of the measures which aim more directly at lowering the blood-pressure the one described first by Maloney[13] and later by Grossman[14] is of the most value. These writers have shown that by means of short periods of mental and muscular relaxation not only temporary, but even longer lasting depressions of both the systolic and diastolic pressures may be attained. This fall in pressure is undoubtedly of the same nature as the one we obtained in the clinic, and which we have described above. However, it seems logical that a greater fall in pressure should be achieved, when we can have a patient lie down in a quiet room, and teach him to relax in mind as well as in body, than when

we simply have him recline on a hard examining table in a noisy clinic, amid strange surroundings. For this is the essence of the Maloney treatment; to teach the patient how to relax by means of repeated lessons on successive days. That is, of course, in line with the general management of the case, and should form a valuable adjuvant. It is particularly desirable to have the patient rest, reclining, for about an hour after every meal.

Drugs are of little help except where there is a specific indication. Of them all, digitalis is probably of the greatest value. Even when the heart is not grossly insufficient, the patient frequently obtains great symptomatic relief, particularly from his sense of fatigue and weakness, and from his headaches, by its proper administration. The nitrites are of very doubtful value. Their effect is so evanescent that it is hardly worth while employing them except during a vascular crisis. Benzyl benzoate has failed to live up to its reputation, and is of no value in reducing the blood-pressure. Many of the patients with hypertension have various nervous complaints, and are fretful and excitable, and sleep poorly. For these some sedative treatment is at times indicated. Chloral and the bromids are of the greatest value in their management.

A review of the subject of hypertension, as presented in this clinic, should, if it does nothing else, teach us with what great caution we must interpret our therapeutic results. The tyro might easily give a patient some drug, and then have him lie down, and take repeated blood-pressure readings, and, finding a drop in pressure, attribute it to the effects of the drug, not realizing that the fall of the readings to a certain level is an almost constant phenomenon. So we must ever bear this variability of the blood-pressure in mind, and before we decide that we have achieved a wonderful therapeutic result be sure to check our findings with serial sphygmomanometric readings, and to exclude as many of the known variables as possible. The general condition of the patient and the functional sufficiency of his circulation are often just as valuable guides as the blood-pressure as to the necessity for further therapeutic interference.

Finally, the essential facts to carry away from a study such

as this are: first, the enormous variability of both normal and abnormal blood-pressure readings; second, that moderate exercise may be followed by a fall in pressure, and finally, that in the study of such a labile phenomenon as the blood-pressure we must be very sure of our ground before we attribute a fall in pressure to any particular therapeutic agent.

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TWO CASES ILLUSTRATING THE CLINICAL SIGNIFICANCE OF UROBILIN. SUMMARY OF OUR PRESENT KNOWLEDGE OF THE SUBJECT.

TODAY you will have an opportunity to study 2 cases that illustrate the significance of urobilin determinations of the urine and feces.

CASE I

Mr. T. (Hospital No. 45,190).

A policeman, aged fifty-five, enters the hospital complaining of weakness, dyspnea, and loss of weight.

His family and past histories are unimportant except that he had malaria some twenty years ago.

During the past three years he has suffered from bodily weakness, numbness and tingling in the fingers of the left hand, and pain in the left shoulder. He has noticed occasional swelling of the feet, which disappeared during rest in bed. He has been transfused with human blood on one occasion which relieved his symptoms for a time.

On physical examination one finds edema of the eyelids, hands, and feet, and marked pallor of the skin and mucous membranes. Other abnormalities are: A soft blowing systolic murmur at the apex, but without cardiac enlargement. Enlargement of the liver to the extent of two fingerbreadths. Slight enlargement of the spleen. The eye-grounds show extreme pallor, but no hemorrhages.

The blood Wassermann reaction and the roentgenologic examination of the stomach and intestines are negative. The red blood-cells number 2,000,000, the white blood-cells 1000, and

hemoglobin 45 per cent. A stained smear shows marked deformity and irregularity of the red cells, stippling, and polychromatophilia. No normoblasts or malarial parasites are found. Of the leukocytes, 67 per cent. are lymphocytes and 33 per cent. are polymorphonuclear. A test-meal shows no free hydrochloric acid and a total acidity of 14. The basal metabolism is increased to the extent of 10 per cent. The blood-serum gives the Gmelin test for bilirubin. The routine urine examination detects no abnormality. *Urobilin and urobilinogen determinations of the urine and feces were carried out on two occasions. The urine contained 1120 dilution units on the first examination and 500 on the second. The feces contained 20,000 and 22,400 respectively.* After several transfusions of human blood the patient's general condition improved, his red blood-cells rose to 3,400,000, and his hemoglobin to 55 per cent.

The above symptoms and laboratory findings are fairly characteristic of so-called primary pernicious anemia. The marked anemia associated with a hemoglobin index greater than unity, the leukopenia associated with a relative increase in the number of lymphocytes, and the absence of free hydrochloric acid in the gastric contents are fairly common laboratory findings in this disease. The only point which I wish to emphasize at the present time is the large quantity of bilirubin derivatives which were found in the *urine* and *feces*.

CASE II

Mr. S. (Hospital No. 42,640).

A retired soldier aged sixty-nine enters the hospital complaining of swelling of the abdomen. His past and family histories are irrelevant except that he imbibed alcohol freely until ten years ago.

His present illness began about four months ago with swelling of the abdomen. Since then about 75 liters of fluid have been removed on five different occasions. He lost from 50 to 75 pounds during the past eight months.

Physical examination shows that the patient is emaciated, the venules of the face are dilated, the pupils react neither to

light nor accommodation, the teeth are carious, and there are evidences of pyorrhea. The heart is somewhat enlarged, but its action is regular and the sounds are clear. The signs of fluid are present over the right lower chest and abdomen. The liver is palpable in the epigastrium and feels granular. The spleen is not palpable. The extremities are edematous. The knee-jerks are absent.

The laboratory findings are: A negative blood Wassermann test, a negative urine, and a blood urea content of 0.22 gram per liter.

During the patient's stay in the hospital about 30 liters of clear straw-colored fluid were removed from the abdomen. His temperature, pulse, and respirations remained normal. His weight decreased by 40 pounds. He was discharged on July 28th, but was readmitted nineteen days later, when 38 pounds of fluid were withdrawn. *At this time the urine contained 188 dilutions of urobilin and urobilinogen and the feces 2400. The former is abnormal, for under normal conditions the urine is practically free from these substances, while the latter is a normal or subnormal amount.* On August 28th a laparotomy for omentopexy was performed, but as no omentum could be found Dr. Whipple was content to suture the abdomen after examining the liver. He states "that the appearance of the liver is typical of Laennec's cirrhosis, *i. e.*, it is atrophic and presents a hob-nail surface." Since the operation the patient has been tapped on several occasions and now he is quite comfortable. No reaccumulation of fluid has occurred in the chest or abdomen for some time.

The results of about 40 urobilin and urobilinogen determinations which have been carried out during the past six months are tabulated below. You will observe that in the first group of miscellaneous cases the urine is usually free from these substances and the amount in the stool is usually under 10,000 dilution units. In the group of hepatic diseases the quantity in the stool is generally not increased, whereas the amount in the urine is relatively large. In pernicious anemia one almost always finds a large increase of urobilin and urobilinogen in the stool and occasionally an increase in the urine as well.

TABLE I

The occurrence of urobilin and urobilinogen in the urine and feces in varying conditions.

Hospital number.	Diagnosis.	Red blood-cells millions per cubic millimeter.	Hemoglobin, per cent.	Twenty-four-hour amount of urobilin and urobilinogen in urine and feces. Dilution units.	
	Miscellaneous Diseases:				
43957	Viridans endocard.......	2.9	60	trace.	7,200
44051	Aest.-autom. malaria....	3.6	50	neg.	8,000
44057	Ac. leukemia...........	1.6	48	neg.	1,400
44203	Carc. pancreas..........	4.1	70	neg.	trace (jaund.)
44193	Bronchopneumonia.....	3.9	70	neg.	4,400
44322	Nephritis..............	2.9	75	neg.	8,000
44351	Purpura...............	4.7	70	neg.	
44496	Catarr. jaundice.........	3.2	70	neg.	2,400
44545	Acute leukemia..........	2.2, 1.3	29	2160, trace.	18,000, trace.[1]
44387	Chronic bronchitis......	5.6	70	neg.	6,000, 7,000
45175		4.7	78	neg.	6,000
45233	Chronic nephritis.......	1.5	35	neg.	10,000
45193	Carcin. liver............	2.1	70	neg.	(jaund.)
45232	Acute rheum. fever.....	5.0	65	neg.	
45404	Carcin. stomach.........	2.3	21	trace.	800
45297	Chr. cardiac disease.....	4.3	80	neg.	4,800
	Hepatic Diseases:				
45434	Liver abscess...........	5.0	70	1,740	
42640	Cirrhosis..............	4.2		188	2,400
41796	Cirrhosis, cholelithiasis..	4.5	92	.....	1,000 (jaun.)
45179	Cirrhosis..............	4.0	80	2,400	
Same case,	Cirrhosis..........	...	..	1,360	22,000[2]
Same case,	Cirrhosis..........	...	..	1,220	16,000
45247	Cirrhosis..............	5.5	80	1,620	8,000
45367	Carcin. liver...........	4.7	80	5,200, 4,760	4,000
45415	Carc. stomach. Cirrhos?.	5.1	65	564	3,840
45511	Cirrhosis..............	4.5	95	2,536	3,200
	Pernicious Anemia:				
44031	Anemia (pernicious?)....	2.0	30	neg.	500,1000,3200
44321	Pernicious anemia......	2.2	70	....	72,000
44433	Pernicious anemia......	1.3	35	544	32,000
44572	Pernicious anemia......	1.7, 1.5	35, 50	tr., 1,056	12,000, 40,000
44657	Pernicious anemia......	..	..	1,524, neg.	20,000, 36,000
40643	Pernicious anemia......	3.8	60	neg.	20,000
44559	Pernicious anemia......	2.0	50	2,200, neg.	32,000, 16,000
45190	Pernicious anemia......	2.0	45	1,120, 500	20,000, 22,000
45398	Pernicious anemia......	1.1	35	400, trace	18,000, 12,000
45506	Pernicious anemia......	1.4	50	2,640	24,000
45596	Pernicious anemia......	3.4	80	1,520	21,200

Urobilin was discovered in pathologic urine by Jaffé over fifty years ago. It is a yellowish-brown or yellowish-red substance of uncertain composition and is probably a condensed and oxidized urobilinogen. The latter, like tryptophan, thyroxin, hematin, bilirubin, and chlorophyll, is a pyrole (C_4H_5N) containing substance and can be prepared in the laboratory by reducing bilirubin with sodium amalgam. It occurs in colorless prismatic crystals, which melt at 192° C. and have a molecular weight of about 600. Fischer has shown that urobilinogen contains at least 2 pyrole rings each connected to different side-chains. It is difficultly soluble in ethyl acetate and benzene, but is readily soluble in ammonia, concentrated hydrochloric acid, alcohol, and chloroform.

In the presence of air (oxygen) urobilinogen is converted into a yellowish-red pigment which gives all the reactions that characterize urobilin. Urobilinogen is further characterized by its reaction with para-dimethylaminobenzaldehyd in hydrochloric acid solution, the so-called Ehrlich's reagent, with which it forms a compound that is easily oxidized to a red pigment in the presence of air. This pigment absorbs certain rays in the yellow and red areas of the spectrum, thus giving fairly definite absorption bands. This reaction is not at all specific for urobilinogen, for it may be obtained with a variety of pyrole-containing substances, but fortunately these are not present in the urine and feces.

Urobilin absorbs certain rays in the blue and green regions of the spectrum. When a urobilin solution is treated with zinc salts a green fluorescense develops. Urobilin also forms a red compound with mercuric chlorid, which is the basis of the so-called Schmidt's test. Urobilin is soluble in ether, chloroform, and alcohol. Fischer obtained about 160 grams of urobilin from

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[1] This patient at first presented the clinical picture of an acute blood crisis. At this time the urobilin and urobilinogen were increased in the urine and feces. Later she gradually developed the signs of an acute lymphatic leukemia.

[2] We have encountered an increased amount of urobilin and urobilinogen in the feces of several cases of advanced hepatic disease. We hope to revert to this phase of the problem at a later time.

a composite consisting of 1005 human stools. His product contained about 66 per cent. of carbon, about 8 per cent. of hydrogen, and about 5 per cent. of nitrogen.

Urobilin and urobilinogen are present in the feces of human beings and all animals except herbivora. For all practical purposes they are absent in the urine and bile except in pathologic conditions. The formation of urobilinogen in the intestinal tract seems to be entirely due to reduction of bilirubin by bacteria. This change is probably quantitative, that is, under normal conditions all of the bilirubin which enters the large intestine is converted into urobilinogen. This change has also been brought about by bacteria outside of the body. The total excretion of urobilin and urobilinogen by the healthy adult is said to be in the neighborhood of 0.1 gram per day; it is directly proportional to the amount of bilirubin which has been secreted into the intestine. In cases of jaundice caused by complete obstruction of the common bile-duct and in profuse diarrhea where the bacteria have not had sufficient time for complete reduction, urobilin and urobilinogen will not be found in the stool.

Under ordinary conditions some urobilinogen is absorbed into the portal system and brought to the liver, where it is retained, if this organ is functionally intact, and according to Addis it is probably converted into hemoglobin. In hepatic disease it may overcome this barrier and escape into the bile or into the general circulation and be excreted in the urine. This may also occur in conditions associated with a marked increase of urobilinogen in the intestine where so much is absorbed that the normally functionating liver cannot retain it. As bilirubin is derived from hemoglobin, or rather from the hematin moiety of hemoglobin, it follows that in conditions associated with rapid blood destruction, as in pernicious anemia, hemolytic jaundice, lead-poisoning, malarial infection, etc., the amount of bilirubin in the feces and, consequently, the quantity of urobilinogen is markedly increased. Most recently it has been observed by Shumm that in these conditions free hematin may be demonstrated in the blood-serum with the aid of the spectroscope.

At present we have no reliable method for estimating the

amount of bilirubin excreted in the bile (as obtained by the duodenal tube), whereas the quantity of urobilin and urobilinogen may be approximately determined. The procedure described by Wilbur and Addis consists of the following steps: First the twenty-four-hour quantity of urine or feces is collected in dark containers, as light exerts a destructive action on these bilirubin derivatives, then an aliquot portion of the urine or alcoholic fecal extract is treated with an equal volume of saturated alcoholic zinc acetate solution, filtered, and mixed with Ehrlich's reagent. The amount of urobilin and urobilinogen is estimated from the number of dilutions which are required for the disappearance of the absorption bands. The average excretion in the stool is about 6500 dilution units (Wilbur and Addis).

Recently Schneider has observed urobilin and urobilinogen in the bile in cases of increased blood destruction. We have been able to confirm this observation on a number of cases, but it is true that cases of pernicious anemia with large quantities of urobilin in the stools may show very little or none in the bile. It would appear as if the examination of the bile alone were insufficient.

The observations of others and our own observations extending over a period of five years have led us to regard the determination of urobilin and urobilinogen as an important procedure in the differentiation of so-called primary from secondary anemia. In the latter condition the rate of blood destruction is usually much lower than in pernicious anemia or hemolytic jaundice, hence the daily output of bile pigments is not markedly increased. In the rare aplastic form of pernicious anemia where the blood-forming organs are principally at fault no increase in the excretion of bile pigment is found. In the Middle West one occasionally sees cases of pernicious anemia associated with subacute combined sclerosis of the spinal cord that show no changes in the blood. It would seem as if blood destruction was going on, but regeneration kept apace without the appearance of immature blood-cells. In this group the urobilin determination may be of signal service.

The determination of urobilin and urobilinogen in the urine

has been used as a test of the functional capacity of the liver. While this is not a fully explored domain, its application would seem to be full of promise Some observers regard the determination as a most delicate functional test. Addis states that "the fact that the hemoglobin-forming function of the liver may show signs of failure while its other functions, such as, for instance, the capacity to convert sugar into glycogen are still carried out without difficulty, . . . so in the special metabolism which is carried on in the liver the rearrangements of the pyrole nuclei required in the synthesis of hemoglobin may be interfered with before the other hepatic functions are involved." We have found, as have others, that urobilinogenuria and urobilinuria are more often found in disease involving the entire liver, such as degeneration in infectious diseases, congestion in cardiac decompensation, or in cirrhosis than in focal processes.

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CONTRIBUTION BY DR. BURRILL B. CROHN

(Based on Private Cases)

EARLY ABDOMINAL SYMPTOMS OF MYOCARDIAL INSUFFICIENCY

The title of this presentation is a vague one, its interpretation rather ambiguous. It is difficult to offer in the few words allowed in a caption a succint and clear description of the symptoms and the disease we are about to discuss. It will soon become apparent that I am not presenting any novel or radical clinical ideas, I am not offering new lamps for old, but am burnishing old ones so as to make them shine more prominently in places poorly illuminated.

By early abdominal symptoms I wish to refer more particularly to those gastric and intestinal (colonic) phenomena that occur so often as aura of impending coronary artery disease and quite constantly accompany this malady when fully developed. As to "myocardial insufficiency" let us understand in this presentation that type of myofibrosis or myomalacia that is dependent upon and associated with diffuse arteriosclerosis and more properly upon degenerative disease of the coronary artery system. Thus, we will, by definition, put artificial limitations about the title and restrict ourselves not to general remarks about abdominal symptoms in all forms of cardiac disease, but, in a word, to the early gastric and intestinal phenomena of the malady which passes under the various denominations of angina pectoris, stenocardia, or coronary artery disease.

An illustrative case will tend the more easily to lead us directly to the point of the discussion.

Case I.—A man forty-three years old, engaged as a bottler of soft drinks, became incapacitated for this work by attacks of

pain in the lower chest and epigastric regions. The attacks were brought about by physical exertion, and were characterized by paroxysms of sharp shooting and cramp-like epigastric pains, accompanied by the belching of large amounts of air and the passage by rectum of voluminous quantities of gas. The paroxysms occurred two to three hours after eating, usually during the digestion of a full meal. The previous history of the patient was devoid of interest. His family life was clean, he denied syphilis, he neither smoked nor abused alcohol. He had been a hard worker, engaged in arduous physical labor since early boyhood. He sought medical aid in many of the cities and clinics of the Middle West. His symptoms were everywhere regarded as abdominal, probably gastric in origin. He was generally advised that his malady was a type of "indigestion" or of intestinal flatulence. He was unrelieved by such advice as he received. At the Mayo Clinic he was told, after careful examination, that they were unable to find any surgical lesion and he was referred elsewhere for medical treatment. The patient was seen by us in New York about one year after the inception of his disease. The first time he was seen he was in the midst of a typical attack. His face was flushed and red, he was perspiring profusely; he held his hands over his epigastrium, complained of severe vise-like pains, and presented the picture of great anxiety. The attack shortly passed over, accompanied by the expulsion by mouth and by rectum of large quantities of gas. Such were the attacks of so-called "flatulence" or "indigestion" from which he was suffering. Throughout the attack his pulse was slow and regular. The similarity of such an attack to a paroxysm of angina pectoris was striking. The subsequent course of the case corroborated this judgment. The patient was put to bed upon Karell diet, with absolute physical and mental rest, much to the disapprobation of himself and the family, who declined to believe that his symptoms, so evidently abdominal, could really be of thoracic origin. In spite of the enforced rest and restricted diet the paroxysms recurred more and more frequently, becoming, after a week, almost continuous. On the tenth day, when just beginning to improve and feel free of symptoms, he toppled over,

instantaneously, dead. Death was probably due to a coronary thrombosis or an embolism into the coronary artery from an atheromatous aortic patch.

In this case the blood-pressure never rose above 140 systolic; his pulse was regular, of fair quality during the period of observation. Renal function was well maintained throughout, his urine containing at times only a trace of albumin. His was a striking example of a stenocardia or coronary artery disease, successfully masquerading for over a year as one of flatulent dyspepsia.

Some time passed before we encountered the prototype of his case. At this time I had under observation a man fifty-eight years old, tall, heavy built, weighing 178 pounds, of serious habit, an individual who in his youth had been a hard and conscientious worker. He had built up by his sole energies a large business, the responsibility of which rested entirely upon his shoulders. In his later years he had become a bon vivant. He ate, at least well, drank beer and wine temperately, smoked heavy cigars in fair number, and kept late hours playing cards for big stakes. He was under observation for a generalized decrescent type of arteriosclerosis, with gradually rising blood-pressure, varying between 160 and 180 systolic, diastolic 90 to 100 mm. Hg. His heart was moderately hypertrophied, a heaving broadened impulse being palpable just outside his left nipple line. The second aortic sound was booming and accentuated. His urine was well concentrated, contained a trace of albumin, and a few hyaline casts. For years his only complaint was that of a sense of tightness or pressure at the top of his head. Urinary excretion was 1440 c.c. per twenty-four hours. Blood urea 22 mg., uric acid 3.1 mg. per 100 c.c. During the last two months he had complained of pressure feelings about the chest and abdomen coming on in attacks after walking on the street or even up a short flight of stairs, or brought on by aggravation or excitement. To these attacks he paid little attention; what he complained of most was fulness of the abdomen, a sense of distention requiring him to loosen his belt, the constant explosive belching of large amounts of air, and the passage, per rectum, of

equally annoying amounts of gas. He was obdurate and insistent that his attacks were due to overeating and indigestion, accompanied by constipation. But his ashen gray facies during his attacks, his spells of cold perspiration standing in beads on his forehead, and his cold clammy fingers suggested as a more plausible explanation the diagnosis of myocardial weakness or coronary artery disease.

The patient scorned all idea of restriction of his activities or of his alimentation, declined advice tending to relieve him of cardiac strain, and persisted in his long hours of administrative work and equally long hours of strenuous recreation. While riding to his business one morning, soon after breakfast, he was seized with an attack and died within fifteen minutes of the onset of the seizure. His ashen gray facies and impalpable pulse and cyanotic extremities betokened a sudden cardiac death.

Let me recount to you another instance of this disease, one in which the intestinal symptoms entirely riveted the attention in the beginning, but one in which the generalized arteriosclerotic phenomena later rapidly strode to the foreground.

The patient was a man of sixty-one years of age. He was previously in good health, mentally occupied in a successful career as a railroad builder. He was the father of a large family. He never suffered from dyspnea, walked one to two miles a day without unusual exertion. He denied lues and used tobacco in moderation. During the last three months he began to lose weight, complained of tiredness, sleeplessness, nervousness, but, above all, of abdominal gas. He had no pain, was not constipated (his bowels moving regularly daily), but he had a constant feeling of tension and fulness throughout his abdomen and passed flatulent gas per rectum during the day. His abdominal distention and flatulence had led him to consult a physician who diagnosed his malady as one of "intestinal stasis and auto-intoxication," and treated him with large subcutaneous doses of autogenous Bacillus coli communis vaccine regained from the stool. His condition became rapidly worse. Distention increased, loss of weight and weakness became progressive. Dr. Weeks of this city being requested to examine the eyes, reported a

complete left-sided hemianopsia with marked pallor of the optic disk. This was the first notice that the disease was other than a purely abdominal functional condition.

At about this time the patient came under my care. The course of the disease was rapid and alarming. A left facial palsy became apparent, the pulse became rapid, slightly irregular at times, and of poor quality. The heart sounds were muffled; much later a true embryocardia or gallop rhythm was superimposed. The liver was palpable and tender three fingers below the free border of the ribs. Blood-pressure 146 systolic and 90 diastolic mm.Hg. It was during this time that the patient had two attacks of typical angina pectoris. His pain was severe and vise-like, precordial in origin, radiating down his left arm, accompanied by angor animi, ashen pallor, etc. Later a right-sided hydrothorax was present for several weeks. The clinical picture was now complete. Beginning purely as a case of abdominal flatulence, the symptoms of a generalized arteriosclerosis rapidly became apparent, as evidenced by hemiplegia, myocardial weakness, coronary artery circulation disturbance, and passive congestion of the kidneys and thorax.

It would ill fit my purpose to burden you with the detailed account of 3 other similar cases taken from personal experience. They are analogous in all respects, now one symptom predominating, now another, but all having this in common, that months or years before the true malignant nature of the malady had become apparent mild gastric and abdominal symptoms had played a prelude which had passed the ken of competent observers.

Let us discuss in more detail some of the phenomena of this insidious malady. The subjects (6 cases in all) were all males between the age limits of forty-three and sixty-one years. It is well known that it is during the fourth and fifth decades of life that we meet with the greatest number of cases showing symptoms of generalized arteriosclerosis and of coronary artery disease. Males always predominate in large proportion. Hard work, physical as well as mental, is a common attribute in all of this series. These men were all heads of families having many

children and having led apparently clean and hard-working lives. They denied syphilis; the Wassermann reaction in the five instances where tested was uniformly negative. Neither gout nor lead enter into the nosologic array of factors, nor does alcohol participate to any great extent as an etiologic element. The same cannot be said to be so universally true of tobacco. One patient was a consumer of five to ten cigars a day, 3 were still more moderate cigar smokers, 1 a moderate cigarette smoker. I should hardly say that tobacco played an important rôle in this series. In a larger series of cases it could hardly have been omitted.

I have not been able to trace any of these cases to a definite infectious origin. Influenza and typhoid as well as rheumatism and, of course, syphilis have been repeatedly pointed out as common causative infective agents producing pathologic changes in the aorta and in the cardiovascular system. It is just now worthy to note that influenza is particularly malicious in this respect, as first pointed out by Sansom and Gibson. In general, the cases observed seemed to result from the wear and tear upon the arterial and the nervous systems incident to the physical and mental efforts of our life of today. Angina pectoris is not a disease that can be well studied in the hospital ward or even the clinic. Private practice is the field, par excellence, for the observation of such cases, since it is only in practice that one is constantly in touch with his patient and the events of the patient's life over a period of years. These cases that I have observed were at that stage in life when a decrescent arteriosclerosis, to use the terminology of Sir Clifford Allbutt, began to become apparent. They were all of them in apparent good health before the onset of the symptoms; the abdominal symptoms were the first sign of arterial disintegration.

The mode of onset varied. We note that in 3 cases the symptoms were gastric. The patients complained of attacks of severe epigastric pressing or cramp-like pains occurring after meals, not with the regularity and rhythmicity of the heartburn of a duodenal or gastric ulcer, but irregularly, often shortly after an unusually heavy meal and not constant in its recurrences.

Yet the diagnosis of peptic ulcer was made by competent observers in 2 of these 3 cases. The pain of an anginal attack is not similar to that of ulcer; it is not a rising crescendo of burning pain with bitter eructations, but it is a vise-like pain accompanied by the belching of gas by mouth. The relief of the pain is associated in time with violent belching which can be heard many yards away. In the mind of the patient the whole attack is one of "acute indigestion," otherwise why could the expulsion of "gas" give relief?

Fractional test-meals give little information, the curves in all instances conforming generally with the normal or hyposecretory types. Emptying time of the stomach was not delayed.

It is this type of case that often comes under the suspicion of being a so-called "acute surgical abdomen." When the attack becomes a prolonged one, and I have seen a status anginosus of the epigastric type, the possibility or the likelihood of a surgical condition comes easily to mind. If, in addition, one has a passively congested and enlarged liver due to impaired myocardial function, the right hypochondriac tenderness added to the pain almost completes the cycle for surgical interference. Much care is required in properly differentiating this type of case.

The other 3 cases in this series had their onset with abdominal symptoms, of which the cardinal one is gas or tympanites. These men complain of fulness, of large abdomen, of being required to loosen their belts soon after and between meals; any effort, such as cough or straining, brings an explosive escape of gas per rectum.

A radical reduction of the diet, particularly the omission of carbohydrates, helps somewhat, but it is not until rest in bed, physical and mental, has been prolonged that one begins to see therapeutic benefit. Constipation usually is associated with the diseases, just as it is with most other conditions of tympanites, but it is not absolutely so. Purgatives and cathartics give little more than temporary relief.

The cardiovascular symptoms vary considerably; most usually the pulse is slow and regular, of good quality, and this may be maintained even throughout a severe stenocardiac attack.

The presence of a myocardial insufficiency may first betray itself by a slight irregularity, a rare extrasystole probably of ventricular origin, or by a diminution of tone in the radial pulse. Such a pulse may become rapid and thready, or the patient becomes dyspneic and ashen gray from the slight exertion of climbing a short flight of stairs. Only later, as the process becomes more manifest, does one see established the real signs of myocardial insufficiency, such as gallop rhythm, fibrillation, muffled heart tones, etc.

The blood-pressure in none of these cases was very high or even more than moderatly above normal.

These cases differentiate themselves early and clearly from the group of cases named by Allbutt "hyperpiesis" or "essential hypertension." Hyperpiesis is recognized clinically by Osler, pathologically by Adami and many others. It is a clear-cut entity, a hypertensive arterial state independent in its inception of pathologic basis, but bringing in its wake cardiac hypertrophy, atherosclerosis, and chronic granular nephritis. This hyperpietic stage is what Huchard meant when he termed it the "presclerotic stage of atherosclerosis."

The cases grouped in this demonstration were not hyperpietic cases. The maximum systolic pressure was 180, the average between 140 and 150 mm. Hg. These cases belong more probably in the group of decrescent arteriosclerosis, arterial fibrosis, or atherosclerosis.

The pathologic process may invade the coronary arteries first, or the arteries of the abdominal organs or those of the brain or kidney. One of this series began with abdominal symptoms, but soon developed hemianopsia and signs of a cerebral thrombosis. Another died with the development of a complete hemiplegia and a uremia. Still another died after a prolonged illness due to a progressive myocardial insufficiency with dilated heart, anasarca, etc.

The pathology of the disease is thus evidenced not alone in the actual cardiac lesion, but also in the concomitant and subsequent phenomena due to generalized arterial changes. In one case a sudden drop of blood-pressure from 150 to below 100

mm. systolic gave the first evidence that there was a cardiac factor as well as an abdominal one to be dealt with.

Cases such as these have been described under the caption of abdominal angina or angor abdominus. Such a case was reported quite recently by Goodman, of Philadelphia. Is there really an abdominal angina, that is, a painful paroxysmal disease associated with an atherosclerosis of the abdominal arteries and aorta? Or are pathologic thoracic stimuli referred by nervous irradiation to the plexuses lying below the diaphragm? Allbutt leans to the view of an independent abdominal angina and quotes cases of typical attacks based upon abdominal aortic aneurysms. He points out that the splenic and pancreatic arterial circuits are the most common ones involved in early atherosclerosis. Osler and Potain and Neusse lean rather to the view that the abdominal symptoms are reflexes from thoracic pathologic processes. I would add my humble opinion to the latter school, for our rapidly increasing knowledge of the interrelation of the general parts of the autonomic nervous system and the clear and succinct explanation of such phenomena by careful clinical obeservers like Pottenger and Head, makes it more probable that the seat of the disease is in the thorax, though reflected "en distence" to the abdomen.

The pathologic explanation of true angina pectoris is still in dispute. The true coronarians, those who see a degenerative process of the coronary arteries in all instances of this malady, seem to have the more convincing arguments at this time. And yet Jenner, who performed the postmorten examination on John Hunter, found a fully previous and patent coronary arterial system, and Cohnheim, Graham-Steele and Osler recount autopsies in which no demonstrable lesion of the coronary vessels were apparent. Allbutt mocks the coronarians and finds the suprasigmoid area of the aorta to be the seat of the disease. Apparently a hypertensive nervous state added to a decrescent atherosclerosis spells angina pectoris, and the explanations of living pathology will have to be added to those of the dead house before the phenomena of the disease are clearly understood.

Some of the abdominal symptoms are occasionally to be

explained on the basis of hepatic congestion with swelling of the capsule of Glisson and consequent nerve plexus strain. When this happens it is a later phenomenon and is probably not present in the earlier stages of the disease. Myocardial insufficiency is the later stage due to myofibrosis, infarcts, thrombosis, etc., dependent upon long-continued coronary atherosclerosis, "cardiopathies arterielle" of Huchard; it is not an early symptom.

The diagnosis of abdominal angina, its differentiation, should be apparent from the recital of the foregoing facts in the paper. Grastric crises of tabes may simulate an angina; so also may renal calculus, cholelithiasis, etc. One new method invites our attention; the electrocardiograph, according to the information of Lewis and of Oppenheimer and Rothschild, gives clear evidence of diminished intraventricular conductivity, so-called "arborization block." Many a case has been saved from a surgical operation by the finding of myocardial weakness as the causative agent of the symptoms. This newer method of examination should never be forgotten.

Regarding prognosis it may be said that the outlook in all of these cases is exceedingly bad. Cases of this kind are serious from the moment that the diagnosis is made. The course that they run is a much more rapid one than that of the usual angina pectoris case. The higher blood-pressure, which seems to act as a compensatory fact in other cases, does not seem to be engendered here. The myocardial weakness is progressive until the point is reached at which the cardiac symptoms far overshadow the earlier prodromal abdominal signs. This stage of decompensation is very often reached within a few months of the making of the diagnosis, providing sudden death does not claim priority.

Treatment.—The general treatment is that recognized by all as the approved treatment for coronary disease, with emphasis upon prolonged bed rest, mental and physical relaxation, reduced alimentation, etc. In most of these cases an active preparation of digitalis administered to the point of physiologic action is apparently very beneficial. The abdominal symptoms are very difficult to relieve and are very obstinate. High rectal enemata and colonic irrigations are of use in relieving the abdominal

distention. The addition of essence of peppermint or of turpentine or of an infusion of chamomile leaves is beneficial where marked distention is present. Cathartics have to be given by mouth to overcome the reflex inertia of the intestines. Magnesia usta or any of the saline laxatives given in the morning in hot water have a prompt action. Unfortunately, they have to be repeated almost daily. Occasionally a daily or a twice daily injection of eserin hydrochlorid, $\frac{1}{60}$ grain, seems to give aid in overcoming atony. The diet should be a restricted though a general one. Protein food is not contraindicated; a definite diminution of starches in the form of potatoes, bread, and cereals should be enforced. Milk should be limited and cold drinks particularly forbidden. As regards the gastric symptoms a prompt diminution of the amount of food intake would promise immediate relief. Antacid medication and carminatives help to a certain degree. The general principles of the whole treatment consists of restriction of diet, particularly of carbohydrates, marked restriction of amounts as well as of fluid intake; mental and physical rest and care of the intestines. The greatest difficulty is experienced in convincing the patient what his trouble really is; that once accomplished, the remainder of the treatment is an easy task. Patients object strenuously to being taken away from their business and the pursuit of their activities because of indefinite abdominal or gastric symptoms, and it is a difficult thing to convince a man that his life is in danger because he belches a bit or suffers from abdominal gas. Prompt measures should follow upon the establishment of the diagnosis. A docile and willing patient will obtain a great deal of improvement in the hands of an experienced physician. One should not fail to curb excesses of alcohol and, more particularly, of tobacco. The latter is important and, particularly in cigarette smokers, often helps to give a long period of remission. A close watch over kidney function is necessary not only from the standpoint of renal efficiency, but as a guide and a judge of cardiac tone and function.

CLINIC OF DR. S. J. NILSON

St. Bartholomew's Clinic

DIET IN ECZEMA

Varieties of Eczema Amenable to Dietic Treatment; Diet in Eczema Due to Uric Acid Retention. Diet When Nitrogen Retention Exists. Diet in Eczema from Food Anaphylaxis.

It is a well-known fact that eczema comprises about one-third of all skin diseases for which medical aid is sought, and it has been a stumbling-block to many clinicians, general practitioners, as well as dermatologists, and up to the present time we have been at a loss as to what to do in some cases of this disease, but in view of recent studies and interest in dietetics many points formerly obscure have now been elucidated.

In the past some writers have taught that a low protein diet is most suitable for patients suffering from eczema, while others have advocated an exclusive meat diet. By various writers the cause of the disease has been referred to ingestion of butter and other fats, oat-meal, fish, etc. Among recent writers, Chipman has called attention to the need of a more intimate knowledge of body metabolism.

There may be some excuse for the many varied ideas on diet. In many instances it matters little whether any one riding a particular hobby, by advocating seemingly unsuitable diet, if the particular patient is able to digest the food advised, provided the elimination is taken care of. Also, it often matters but little what the diet consists of; an exclusive peach diet in the summer for a number of days may prove to be a marvelous cure, but that doesn't necessarily mean that every patient should be put on a peach diet, but make the diet of sufficiently low caloric value, and at the same time taking care of the elimination, then

you have struck the keynote on which to build success in this disease.

Though the majority of cases of eczema will respond to dietetic treatment, there are others in which such treatment seems of little avail except to improve the patient's general health.

Before employing any dietetic measures in many skin diseases, particularly in eczema, one should always bear in mind the varying factors influencing digestion, which comprises investigations as to the pathologic alterations of the digestive tract, as well as the other organs concerned in digestion, such as the liver and pancreas. The other organs to be considered in this connection are those of excretion, such as the sweat-glands, lungs, kidneys, and the large intestines, bearing in mind any alterations in the cardiovascular system which might have an important influence on the digestibility of foods; one can then easily see that the coefficient of digestibility is influenced by these various factors, and that digestion does not consist merely of the study of calories, as caloric values vary, as can readily be seen by the above-mentioned influencing factors.

Varieties of Eczema Amenable to Dietetic Treatment.—In a general way it seems to me from clinical observation that there are three classes of eczema amenable to dietic treatment, namely:

1. Eczema occurring in individuals who have retention of uric acid, or of nitrogenous excretory products.
2. When food anaphylaxis is present.
3. Eczema of infants and young children. At this time we will confine ourselves chiefly to the first two headings.

Diet in Eczema Due to Uric Acid Retention.—Uric acid retention is of frequent occurrence in eczema and is often seen in apparently healthy, robust adults. These individuals usually have a gouty diathesis and uric acid retention. Eczema of this type may be localized, consisting perhaps of a papulovesicular eruption of the hands, or it may be a generalized condition. If failing to cure this with local treatment, dietetic measures should be employed.

The diet in this type should be essentially one that is purin free and of low protein content. Food rich in nuclei, hence in

purin, such as pancreas, thymus, liver, and kidney, should be excluded. Malt liquors, tea, coffee, and chocolate contain purin, while, on the other hand, green vegetables, milk, and eggs are purin free.

In many of these cases it takes a long time before any appreciable effect is noticed on the lesions and diet has to be continued persistently for several months. In other cases it is but short of marvelous how rapidly the lesions do clear up.

A good procedure is to put the patient on a diet of buttermilk, soda biscuits, milk crackers or toast, and orange or lemon juice from the ripe fruit for three days or longer, according to the severity of the case as governed by the rapidity of the disappearance of the lesions. Use 2 quarts of buttermilk, 8 milk crackers or 4 slices of toast, 3 or 4 oranges or lemons. This will yield from 1200 to 1400 calories. Alternate buttermilk with the fruit juice at intervals suitable for the individual patient. In addition, give an alkaline salt, as 1 to 2 drams or more of bicarbonate of soda per day, taken in fruit juice or in plain water.

Sweet milk may be substituted in about half the quantity of buttermilk if, for any reason, buttermilk cannot be taken, as the caloric value is about double that of buttermilk. You may add to the sweet milk either barley-water or lime-water. Gradually, well-cooked cereals or two or three slices of bacon, later soft-boiled eggs, stewed fruits and vegetables, as spinach, celery, etc., are added to the diet. Later, potatoes, butter, and meats are allowed, keeping constantly in mind the need of stopping at a point at which a relapse occurs. Meat may be restricted to a certain number of days a week.

Diet When Nitrogen Retention Exists.—Under this group we have to consider nephritic conditions. In the first place comes eczema, occurring in connection with acute nephritis. The treatment consists of the usual measures for the relief of this condition, where the Karell or other suitable diet should be instituted.

However, the type with which we have to deal is usually the more chronic one, in which retention is present. Then we have eczema occurring without nephritis being present, but where the

nitrogen retention occurs independent of it. In either case it is well to obtain an accurate knowledge of the condition of the kidney function. This can be done by careful examination of a twenty-four-hour specimen of urine or by examination of the blood, estimating urea nitrogen, uric acid, and creatinin, or by the various functional tests, as that by phenolphthalain or by test-meal.

In applying the diet in the nitrogen retention cases our aim is to give a low protein diet if anaphylaxis can be ruled out, first giving sufficient fluid to free the system of the nitrogenous excretory products. This is best given in the form of water with orange juice or an alkaline salt, such as a combination of potassium citrate, acetate, and bicarbonate, 30 grains each, three times a day. After this we can give the rice diet, consisting of rice boiled in water and well dried out, eaten with butter and dry bread, three times a day. It should be thoroughly masticated and incorporated with saliva. If, for any reason, the rice diet does not agree, a buttermilk or sweet milk diet, as before mentioned, can be instituted. In case of the rice diet, which can be continued from three to five days or longer, then milk can be added for a few days, gradually adding other food, such as vegetables; at first a varied vegetable diet can be continued for a comparatively long time, gradually adding a moderate amount of meats. It is important to bear in mind that sufficient quantities of water, preferably taken two hours after meals, should be insisted upon, this quantity being determined according to the findings in each individual case. Exercise is also of importance, and should be insisted upon, as this increases oxidation and aids in the elimination of waste products.

Diet in Eczema From Food Anaphylaxis.—The second class of eczema involves a careful investigation as to the underlying cause, inasmuch as we have to deal with a food anaphylaxis. This is a condition of unusual sensitiveness or an exaggerated susceptibility to foreign protein, as shown by White, Strickler, and others.

A great deal of work on food anaphylaxis has been done by the cutaneous test and a good deal of light has been thrown upon

the subject, but we need further elucidation for uniform results. These tests have proved very unsatisfactory in young children. Infants do not react well to the test and so far have been found to be of no value. In adults, several points have to be considered in applying the tests. for instance, an individual who has an eruption caused by strawberries may give a negative test out of season, or when they have not been eaten for a long time. Now, if you feed this individual strawberries, the reaction will often prove positive. The same is true of many other foods.

The offending food substances, which in all probability are proteins, must be ascertained. It is always desirable to obtain the history of eruption occurring in childhood, as this often gives a clue to work upon. If sensitiveness is present, it is most often due to two or more proteins. The common ones are milk, egg-albumen, wheat, buckwheat or some other grain, or shell-fish. Less common are meats, as pork, veal or mutton, and tomatoes.

There are two ways in which to identify the offending substance: (*a*) The diet test; (*b*) the endermic or cutaneous test. In the first method the patient is put on a mild diet which we know will not cause any disturbance, gradually adding the above-mentioned foods one at a time until reaction is obtained. This food is then eliminated from the diet and other articles of food are similarly tested. This process takes a long time and requires careful observation both by the patient and physician.

The second method consists of endermic injections of a definite dilution of foreign proteins. A positive reaction consists in the development of (*a*) An erythema; (*b*) a papule; (*c*) tenderness. Reaction is shown by a lesion usually $1\frac{1}{2}$ to 2 cm. in diameter, lasting forty-eight hours. This method requires a careful technic, because unless properly carried out it is extremely dangerous, and has proved fatal in a number of cases.

The safest method of performing the skin test is to denude the superficial epithelium in two parallel rows on the forearm; areas denuded depend upon how many proteins are to be tested, 12 to 24 proteins can readily be tested at one sitting, more if desired. The areas can be denuded by a dental burr, without

drawing blood, or by a small incision with a scalpel, one row in each case being used as a control. The proteins are applied to the other row and rubbed in after applying neutralizing medium, sodium hydroxid being usually used for this purpose. A positive reaction is indicated by an erythema and a wheal from ½ to 2 cm. in diameter appearing within fifteen to twenty minutes. This method is fairly satisfactory.

The offending foreign protein having been discovered, it is eliminated from the diet, or fed in small increasing quantities until anti-anaphylaxis is produced. This condition is not an immunity and may be lost unless the protein in question is continued.

It is also well to control the carbohydrate and fat digestion and to maintain a proper function of the large intestine. In acute cases more care is required than in the chronic ones. It is best to exclude food which is difficult to digest, such as pastry, foods fried in grease, and fat soups. Coffee and tea should be limited to one cup in the morning.

CLINIC OF DR. S. NEUHOF

LEBANON HOSPITAL AND CENTRAL AND NEUROLOGICAL HOSPITAL

AURICULAR FIBRILLATION

Clinical Diagnosis; Varieties and Manifestations; Physical Signs; Therapy and Its Results.

CASE I.—DISCUSSION OF AURICULAR FIBRILLATION, WITH AN ILLUSTRATIVE CASE

DR. NEUHOF: THIS man is forty-five years of age. The previous history states that at the age of three he had some bone infection in his left knee which resulted in an operation and subsequent fistula. There is no history of any other infection—no growing pains, no scarlet fever, no rheumatism, no sore throats except one very mild one which lasted a day or so. He gives a moderate alcoholic history. There is nothing otherwise in the history which has any relation to his present trouble. The Wassermann blood reaction is negative.

The complaint which brings him to the hospital began rather acutely about five months ago. He then became short of breath; he could not walk; his abdomen began to swell.

Let us first study the heart action. Please listen to the heart, not for murmurs at present, but with the primary idea of telling me what you think of his arhythmia.

STUDENT: There is very rapid, irregular heart action, the first sound seems to be very strong.

DR. NEUHOF: For the present I am interested in the rhythm alone.

FIRST STUDENT: The rhythm is irregular, rapid, and at times seems to be skipping.

SECOND STUDENT: His heart is very irregular; first it is slow, then rapid, then it skips.

THIRD STUDENT: It seems paroxysmal.

Dr. Neuhof: I notice, in the first place, that none of you gentlemen felt the patient's pulse; that in itself is a very grave error. Every time that you examine a heart, particularly when studying and looking for arhythmias, always feel the pulse at the same time. If you do that in this case you will notice not only that the heart action is irregular but that the pulse is also; furthermore, with every heart-beat there is a pulse-beat; that is, the pulse is just as irregular and as rapid as the ventricular action. You will further note that there is not only an irregularity in time but also in the strength of the ventricular beats. There are scarcely two successive beats of equal force or rhythm.

The type of arhythmia which produces such gross irregularity of force and rhythm of the heart and a corresponding irregularity of the pulse is called auricular fibrillation.

There are various experimental methods by which auricular fibrillation can be produced. A common method is to faradize the auricles directly. As a result, instead of having the physiologic orderly rhythmic auricular contractions followed by regular systolic contractions of the ventricles, there results irregular discordant auricular activity. Different parts of the auricle contract at different times and with varying intensity; indeed, as the term denotes, the auricles actually fibrillate. At the same time the auricles are in a state of dilatation. What is the result of this upon the ventricular activity? In the normal rhythmic heart, as you know, the impulse starts at the sino-auricular node, the so-called pace-maker, and spreads thence through the auricle to the auriculoventricular conduction system. The latter consists essentially of the auriculoventricular node, and of the bundle of His with its branches. The ventricles are thus incited to rhythmic orderly contraction. In auricular fibrillation there is, as it were, a bombardment of the conduction system by auricular impulses. As many as 900 of these per minute have been counted in the electrocardiograms of a patient with auricular fibrillation. Comparatively few of these impulses can pass through the conduction system. Those which do pass incite the ventricle to irregular, tumultuous activity. That is true in the case we are studying. Indeed,

because of this man's thin chest wall and enlarged ventricles you may actually see that the ventricular contractions are irregular in strength and rhythm. One may even venture a diagnosis of auricular fibrillation by mere careful inspection of the cardiac area. Please remember that you never see or hear the auricles fibrillate, but that you make the diagnosis of auricular fibrillation by the characteristic effect of the latter upon ventricular activity.

What is the result of this irregular ventricular activity upon the systemic circulation? Some of the ventricular contractions are so weak that they cannot open the aortic valves and therefore cannot produce corresponding pulse waves in the radials. Another reason for the non-opening of the aortic valves may be that the ventricular systoles, otherwise sufficiently strong, do not properly direct the blood toward the aortic valves. In either case it is apparent that there will be more heart-beats than pulse-beats. The consequent lack of correspondence between the number of ventricular systoles and the pulse-rate is sometimes called pulse deficit. I prefer the more descriptive name of abortive beats. The stronger ventricular systoles open the aortic valves in the usual fashion and produce correspondingly strong pulse-beats. But since even these effective ventricular systoles vary in force and rhythm there is a corresponding variation in the propagated arterial waves as shown by a pulse which is also irregular in force and rhythm.

Let us verify all these observations by again examining the patient. You will note that some ventricular systoles are followed by pulse-beats, while others are not. I wish to impress upon you again that this simply results mechanically from the fact that some of the ventricular systoles do not open the aortic valves.

Why do patients with auricular fibrillation so frequently decompensate? It has been shown experimentally that the reason depends primarily upon the resultant irregular ventricular activity. When the latter is present the blood cannot be thrown into the systemic circulation in an orderly fashion, and it is this

which finally produces what we call heart failure or decompensation in patients with this arhythmia.

Clinically, the incidence of auricular fibrillation may be roughly grouped as occurring first, in *rheumatic endocarditis;* second, in *cardiosclerosis;* and third, in patients *without cardiac disease*—the extracardiac group. All these groups will be discussed in detail in succeeding clinics. Here I wish to state briefly that the rheumatic valvular lesion most apt to produce auricular fibrillation is mitral stenosis. Further, that by cardiosclerosis I mean a generic term which includes gross pathologic changes in all the cardiac structures—valves, endocardium, muscle, aorta, and coronaries. It occurs chiefly in older individuals with general arteriosclerosis, with or without hypertension. The third group—those without actual cardiac disease —is the smallest in number.

Auricular fibrillation comprises approximately 80 per cent. of all arhythmias, hence the importance of understanding and diagnosing it. Besides it will be much easier for you to grasp and comprehend the others if you thoroughly recognize this irregularity. Another practical reason why it is so important to grasp the fundamentals of auricular fibrillation is that it is the one which may most often be benefited therapeutically. We know that digitalis has the power of blocking many of the discordant auricular impulses which bombard the auriculoventricular conduction system in auricular fibrillation. These impulses are thus to a great extent cut off, so that the ventricles are restored to some condition of orderliness in rhythm and force. In addition, digitalis also helps by increasing the contractile power of the heart. Its great advantage, however, in fibrillation arises from the aforesaid power to block the manifold auricular impulses, thereby producing more regular heart action.

Thus far we have concerned ourselves only with the general diagnosis of, and the problems arising from, the arhythmia itself. I should now like to have you listen to the heart with a view to distinguishing the abnormal sounds you hear.

First Student: The sounds are accentuated; there is a murmur.

Second Student: The first sound is replaced by a loud murmur; a systolic one. I do not think the second sound is accentuated.

Third Student: There is a murmur which seems presystolic, and at the same time one hears a sharp first sound. The second sound is accentuated.

Dr. Neuhof: Upon auscultation I find as follows: In an area surrounding the left nipple I hear a rather loud systolic murmur. A little lower and near the cardiac apex I hear a somewhat distant diastolic murmur which occupies the last half of the diastolic period. Will you please listen now in order to corroborate these auscultatory findings?

The patient's heart action was so rapid when first admitted to the hospital and before putting him on digitalis that no murmur could be distinguished. But, as I have just pointed out, we now hear in the left nipple region a rather loud systolic murmur, and in the apical region a relatively distant diastolic murmur of a somewhat rumbling character. In the presence of auricular fibrillation these are typical of a double mitral lesion: the systolic, of mitral regurgitation; the diastolic, of mitral stenosis.

And now as to the size of the heart. Even without percussion you note the size of the organ as it is silhouetted against the chest wall. The apex is in the fifth interspace in the axillary line.

The liver is enlarged; its lower border can be felt at the umbilicus. There is very slight edema at the ankles.

Let us now search the history for the cause of the valvular disease in this patient. The great majority of cases of mitral disease are caused by rheumatism, tonsillitis, or scarlet fever. The patient says he had a slight attack of sore throat some months ago shortly before his cardiac symptoms began. Such wide-spread cardiac mischief, however, could not possibly have been produced by so recent and mild an attack. It is possible that this patient represents one of those in whose childhood there had been so-called "growing pains"—in other words, rheumatism,—and that the patient does not recall them. Or the old bone infection in childhood may be the cause of this mitral lesion. Under such circumstances, however, patients are not apt to have

such exceedingly long quiescent periods, for, as you remember from the history, this man until recently never had any cardiac symptoms. Indeed, he had never consulted a doctor about his heart until a few months ago, a very unusual story of an endocarditis resulting from a septic bone infection. With reference to the alcoholic history in this case, he has been only a moderate drinker. The rôle of alcoholism as a cause of endocarditis has been, as we now know, overemphasized; and, even conceding alcoholism as an etiologic factor, it is difficult to conceive it as producing such a typical mitral valvulitis. Weighing all probabilities, it seems most likely that the cause of the lesion is rheumatism, the details of which the patient has forgotten.

This patient has received altogether a little over 2 drams of the tincture of digitalis. The drug has already produced a very marked change in his condition. The heart beats less frequently and there is a greater tendency to regularity. The edema of the ankles is less; the liver is smaller. The man can breathe comfortably, and he says he "feels fine." He would scarcely have to tell us that, because a cardiac patient who breathes as comfortably as he does always "feels fine." I am now going to put him upon rather large doses of digitalis, $\frac{1}{2}$ teaspoonful three times a day for about three days, and then for the following two days upon theobromin sodium salicylate with a limited fluid intake.

Regarding further care of this and similar cases I should advise that after compensation has been restored the patient consult a physician about every two or three weeks. We know that, given properly, digitalis may be taken for a number of years. This patient may be made so comfortable that he may even be able to follow some light pursuit. Some become so accustomed to taking digitalis that they themselves are able to approximate the proper amount of the drug needed. The average amount of the tincture of digitalis required to restore compensation is 1 ounce. I am in the habit of giving 1 dram a day in the usual mild cases of decompensation with auricular fibrillation. In more urgent cases I prescribe much larger initial doses.

STUDENT: Does the pulse-rate influence you in the amount of digitalis to be given?

DR. NEUHOF: If I do not get the proper effect—that is, the restoration of compensation—I would continue digitalis up to the 1 ounce amount even though the ventricular rate were to fall as low as 45 per minute. As a matter of fact, in order to investigate that point for myself I had under observation some three or four years ago a series of cases of fibrillation in which I continued digitalis despite the fact that the ventricular rate was between 40 and 50 per minute. One patient told me he had never felt better in his life. He left the hospital with a heart rate of 35 per minute.

STUDENT: How often would a case of this sort have to be seen in private practice?

DR. NEUHOF: Ordinarily once daily while in the acute stage. As the patient's condition improves, say at the end of four or five days, he may be visited less frequently.

STUDENT: Do you give tincture alone?

DR. NEUHOF: I always give the tincture alone and undiluted. You can keep a good tincture several months without deteriorating.

STUDENT: How long do you keep such a patient in bed?

DR. NEUHOF: That depends on the severity of the case. This particular patient will probably improve sufficiently in about ten days so that he will then be able to sit out of bed, and in a few days thereafter walk around.

STUDENT: Does he feel very weak?

DR. NEUHOF: The usual complaint is shortness of breath. The weakness is not more marked than that of other bed-ridden patients. If I allow this patient to get up and walk around without continuing digitalis in smaller doses he will decompansate in a comparatively short time, probably in several weeks. Incidentally, what I have just said proves to you that the old theory of the danger of continuing digitalis when a patient is walking about is an erroneous and exploded one.

CASES II, III, IV.—DISCUSSION, DESCRIPTION, AND TABULATION OF VARIOUS TYPES OF AURICULAR FIBRILLATION—ILLUSTRATIVE CASES

Today I wish to continue the subject of auricular fibrillation and shall illustrate it with several additional cases.

Case II.—This patient has already been examined by some of you. M. H. is a typical example of a decompensated double mitral lesion with auricular fibrillation. You will recall that I advised the continuation of medication even after compensation was restored. He has not taken any digitalis since he left here three weeks ago; he re-entered the hospital several days ago decompensated and dyspnoic. Two or three days after the second admission he developed a left-sided hemiplegia; you see he cannot raise the left arm or left leg. Upon listening to his heart you hear, just beneath the left nipple, a loud systolic and a distinct, though somewhat distant, diastolic rumble followed by a reduplicated second sound. The pulse and heart action are grossly irregular in force and rhythm. The liver is enlarged; there is no edema of the legs. This case, therefore, represents auricular fibrillation with a double mitral lesion probably due to an old rheumatic infection.

The prognosis is now complicated by the hemiplegia, which no doubt is due to an embolic infarct from one of the mitral vegetations. The point I wish to emphasize at this juncture is that the patient did not follow my directions regarding digitalis. I had stated that despite the fact that he was thoroughly compensated when he left the hospital, he would have to continue medication. This patient did not do so, and I am therefore not surprised to find that he returned very much decompensated. It is, indeed, probable that the irregular violent ventricular action such as is even now present was the controlling mechanical factor which loosened one of the mitral vegetations. If the heart had been beating more quietly and less irregularly under the influence of digitalis an embolic infarct would have been less likely to occur.

Case III.—A. B., male, seventy-six years old, came to the hospital for a skin disease which has no connection with his

cardiac status. I wish to demonstrate him as illustrating a cardiac type very frequently found among the old and senile. He has emphysema and he also has a very irregular pulse. I want you to feel his pulse and to listen to the heart at the same time—a procedure always to be followed when studying arhythmias. You will find that unless the patient sits up you can scarcely feel the heart beat. The sounds are very faint, probably because the organ is covered by emphysematous lung. The radial and temporal arteries are thickened. You note that the pulse is irregular both in rhythm and force, an almost infallible sign of auricular fibrillation. The underlying pathologic lesion is cardiosclerosis, a very frequent finding in elderly individuals. Very often such patients have no cardiac symptoms. In this case, for example, despite the fact that the pulse is grossly irregular, there are absolutely no cardiovascular symptoms—no dyspnea, no edema, no decompensation.

Case IV.—This man, fifty-three years old, a tailor, tells us that except for very slight, temporary ailments he had never been ill until five years ago. At that time he sought admission to another hospital and stayed there for two weeks. The symptoms then were shortness of breath and cough. He left the hospital and soon thereafter noticed that his eyes began to bulge, although he felt absolutely well and was able to continue at work for several years. He then sought readmission to the same hospital because of recurrence of the original symptoms. After several weeks he left and was again well until about six weeks ago. At that time he developed diarrhea and shortness of breath. The latter has continued up to admission to this hospital five days ago.

Let us now examine the patient. First, by inspection you note that the patient is very dyspneic and that he has very marked exophthalmos. You further note very prominent and irregular pulsations in the neck; the larger and more vigorous are due to the carotids. The jugular pulsations are irregular, but less prominent. You likewise observe that there is a fulness of the neck in the region of the thyroid; both lobes of this gland are considerably enlarged. In the chest you observe that the apical

impulse is diffuse and is very rapid and irregular in the time and force of its systoles.

Second—palpation: By placing the palm of the hand over the precordium you are able to feel and corroborate what you have just observed by inspection; namely, the diffuse irregular impact produced by ventricular systoles which are irregular in rhythm and force. In other words, the ventricular action is grossly arhythmic. No thrill is felt over the precordium.

Third—auscultation: We hear no cardiac murmurs, but we do hear some moist, crepitant râles probably due to congestion and edema of the left lung. You also note that some of the ventricular beats do not reach the wrists. That is due to the fact, already pointed out in a previous clinic, that some of the systoles are not strong enough to open the aortic valves or that they do not throw the blood in a proper direction toward the aortic orifice. Either reason is sufficient to prevent opening of the valves and hence prevents a corresponding pulse wave.

Finally—the size of the heart: The apical impulse is most prominent in the sixth interspace, 12 cm. from the midsternal line, a point near the anterior axillary line.

The liver is considerably enlarged; its lower border is 2 inches below the umbilicus. There is marked edema of the legs. The urine shows hyaline and granular casts. The Wassermann blood-test is negative. Regarding therapeusis, I wish to mention that, despite digitalis, morphin, and bromids, all given in large doses, there has been no improvement in the patient's condition.

This case is one of auricular fibrillation as determined by the absolutely irregular ventricular action. Because of the exophthalmos, the enlargement of the thyroid, the absence of any rheumatic or infectious history, the sharp attack of diarrhea antedating the present illness, and because the patient had several attacks of decompensation, I believe that the auricular fibrillation and consequent heart failure are due to exophthalmic goiter ("Basesdow's disease"). I shall shortly explain my reasons for this view.

I ask you now to study this tabulation with me, in which I divide the subject of auricular fibrillation as follows:

TABLE I

A. *Experimental Causes of Auricular Fibrillation.*

1. Stimulation of the vagus.
2. Stimulation of the sympathetic.
3. Direct faradization of the auricles.
4. Injection of thyroid extract intravenously. (One experiment.)

TABLE II

B. *Some Abnormal Factors Found in or Productive of Auricular Fibrillation in the Human Being.*

1. Enlarged and dilated auricles.
2. Pathologic changes in the pace-maker (sino-auricular node).
3. Changes in nerve tone in the pacemaker:
   (*a*) From destruction of nerve fibrils and ganglia.
   (*b*) From abnormal impulses reaching the pace-maker.

TABLE III

C. *Auricular Fibrillation is Found Clinically in:*

1. Cardiovascular disease:
   (*a*) Valvular disease—chiefly mitral stenosis.
   (*b*) Cardiosclerosis—chiefly senile.
   (In both, auricular fibrillation is usually permanent.)
2. Extracardiac causes in patients with normal and abnormal hearts:
   (*a*) Toxins:
   Biologic—chiefly in pneumonia.
   (A. F.[1] usually temporary.)
   Chemical—tobacco, sulphuretted hydrogen.
   (Isolated observations.)
   (*b*) Reflex—chiefly from gastro-intestinal disease.
   (A. F.[1] usually temporary.)
   (*c*) Exophthalmic goiter.
   (A. F.[1] usually in attacks or permanent.)
   (*d*) Drugs—chiefly digitalis. (A. F.[1] usually temporary.)
   (*e*) Emotions—fright, fear, excitement. (A. F.[1] in attacks.)
   (*f*) As part of or during attacks of paroxysmal auricular tachycardia.

[1] A. F. = Auricular fibrillation.

I assume that you know what I mean by the pace-maker, the normal rhythm center, or the sino-auricular node—all interchangeable terms. You know that its arterial supply is a rich one, the node being supplied by its own special artery. It is also rich in nerve ganglia and fibrils.

I want to stress the importance of the knowledge we now possess, that fibrillation may be temporary or may appear in attacks. The older writers regarded auricular fibrillation as a perpetual arhythmia.

You of course observe that Cases II, III, and IV—all fibrillators—belong in different etiologic categories. I shall briefly discuss some of the clinical conditions in which auricular firbrillation is found.

Mitral stenosis is one type of valvular disease in which fibrillation is quite common. Usually in decompensated mitral stenosis, in which fibrillation has appeared for the first time, the ventricular action is quire irregular, and the rate 100 per minute or more. Decompensation, as I have already emphasized in a previous clinic, is brought about by the irregular ventricular action which results from fibrillation, and it is this which is of such extreme practical importance. That is to say, the thing which disturbs the patient clinically, which causes the dyspnea, the anasarca, the bronchitis, etc., is the irregular ventricular activity which prevents the blood from being thrown into the general systemic circulation with any degree of regularity.

Senile cardiosclerosis, another type, is also frequently accompanied by auricular fibrillation. It is by no means rare to have, as in Case III, rather irregular heart action with rates which do not exceed the normal ventricular rate. The pulse and cardiac irregularity, if you will recall the examination of Case III, is not nearly as marked in rhythm or force as, for example, in Case IV, thepatient with the exophthalmic goiter. That probably accounts for the fact that patients such as the former do not often suffer from much disturbance in the sytemic circulation despite fibrillation. Case III, indeed, came to the hospital for an entirely different disease; the irregular pulse was only an incidental finding. There are, however, senile cardiosclerotic cases which

do have very irregular heart action with fibrillation, and those are the patients who suffer most from dyspnea and other signs of decompensatory disturbances.

We shall now discuss, in conjunction with Case IV, the question of exophthalmic goiter with auricular fibrillation. By correlating the tabulated experimental (Table I) and the probable fundamental causes of fibrillation (Table II), we may be able to find the cause of the fibrillation in Case IV. I want to preface, however, that what I am going to tell you about fibrillation in exophthalmic goiter is to some extent hypothetic, because, although we have some experimental data, the facts are not sufficiently known to enable us to draw exact clinical conclusions.

You note from the Table that, experimentally, stimulation of the sympathetics has produced auricular fibrillation, and clinically, that changes in the rhythm center may also produce fibrillation from abnormal impulses reaching it. We know that exophthalmic goiter is sometimes accompanied by mild pathologic changes in the myocardium; in rare and exceptional instances these may amount to extreme cardiac hypertrophy without involvement of valvular or arterial structures. Furthermore, exophthalmic goiter is almost invariably accompanied by evidence of excitation of the sympathetic system. Observe, for example, the usual tachycardia and sweating in exophthalmic goiter. We know, also, that there are undoubted instances in which sudden emotions, such as fright and excitement, were the starting-points of exophthalmic goiter. Case IV states that preceding his last attack of cardiac failure he had severe diarrhea having no relation to diet and uncontrolled by medication. I believe that this symptom—intestinal hypermotility—was another evidence of hyperexcitation of his sympathetic nervous system.

To summarize: The goiter, the exophthalmos, the fibrillation with consequent decompensation, and the diarrhea are the results of disturbances of the sympathetic system. I profess, however, no knowledge as to the fundamental cause of the sympathetic disturbance in this case. Regarding therapy, I am not surprised that digitalis has not had the slightest effect upon

the irregular and rapid ventricular activity or upon the heart failure. We have no specific, nor anything like a specific, at present which can influence continued fibrillation in patients with goiter. The primary therapeutic effort must be directed toward some drug which can control the hyperexcitable sympathetics. I have tried digitalis in several other cases of goiter with fibrillation and heart failure without benefit.

The discussion of Case IV shows the importance and need of correlating all factors and data in the study of the individual cases of auricular fibrillation which you may be called upon to diagnose and treat. If a case of decompensation is due to auricular fibrillation with mitral stenosis you will find, with few exceptions, that digitalis acts almost as a specific. I prefer to give the tincture as already outlined in a previous clinic. I want to emphasize again the importance of keeping such cases for an indefinite period of time under the influence of this drug, otherwise they will again decompensate. Case II is an excellent example of that fact.

Let us now take an instance of auricular fibrillation in senile cardiosclerosis with fairly marked irregular and rapid ventricular activity and with signs of decompensation. There again digitalis will probably have a beneficial effect. I say "probably" because one must understand that in senile cases there are usually advanced pathologic changes in the myocardium, endocardium, and the coronaries, thus there is often not enough healthy heart left upon which the digitalis can act. Such advanced changes constitute, I believe, the most potent reason for disappointment in the action of digitalis in these individuals. Digitalis may indeed block the discordant impulses coming from auricle to ventricle in fibrillation, and hence help steady the ventricular action; but it cannot very well increase the contractile power of a considerably damaged heart.

I shall now briefly discuss some of the salient extracardiac causes of fibrillation in patients with otherwise normal hearts. Some years ago I observed a case of fibrillation without dyspnea in a tobacco smoker with an organically sound heart. A similar case has been reported in the literature. An instance of transient

auricular fibrillation has been reported in a laborer who while working in a vat was overcome by hydrogen sulphid gas; his heart was organically normal. We also occasionally observe patients with absolutely normal hearts, blood-vessels, and kidneys who apparently set up fibrillation as the result of reflex causes arising from stomach or intestinal disturbances. An illustrative case is the following: About two years ago I was consulted by a lady fifty-nine years of age. She had been suffering from belching and regurgitation of food for many years. About ten years ago she had colitis and abdominal cramps. Five years thereafter she had pains over the sigmoid. She was operated upon for appendicitis. Adhesions were found; the pains over the sigmoid persisted. During the past summer she was considerably oppressed by the heat. She went to Atlantic City, and while resting in a rolling chair she had a fainting spell lasting about five minutes. Her family physician, an excellent and careful practitioner, assured me that the summer before her pulse had been perfectly regular. I saw her some weeks after the fainting attack; the pulse and heart action were grossly irregular; sometimes slow, sometimes fast. She had attacks of tachycardia during which the heart rate was over 160 per minute; its rhythm was irregular. Only at such times was there slight dyspnea. At other times the patient complained of a subjective feeling of "palpitation." The gastro-intestinal symptoms consisted of belching, colicky pains, and intestinal rumbling. A polygraphic tracing which I took revealed auricular fibrillation. In the absence of any evidence of organic cardiac disease—no decompensation, no edema, no bronchitis, no cyanosis, no hypertension, no abnormal constituents in the urine, no cardiac enlargement, no murmurs—and because of the old though still present gastro-intestinal symptoms, I made the diagnosis of auricular fibrillation arising reflexly from the gastro-intestinal canal. Therapy was directed chiefly to the latter. Bromids were prescribed. A good prognosis was given, although no time limit was set as to the duration of the fibrillation. The patient was allowed to sit out of bed, then to walk, and gradually to resume her old activities, even including golfing, The arhythmia lasted several

months. The pulse and heart action finally became regular and remained so. This case is given in detail partly because of its interest, partly to impress upon you the great importance of obtaining a good, careful previous history, and finally, the importance of studying, correlating, and weighing all data before arriving at a diagnosis.

Returning to Table III, you note that auricular fibrillation may occur as part of or during an attack of paroxysmal auricular tachycardia. The latter means that the auricles are beating regularly at a rate between 180 and 250 per minute. The ventricles may beat at the same speed or not, depending upon whether the ventricle responds to every auricular impulse. When the ventricle does not regularly respond it denotes that heart-block is present. It is not unusual to have paroxysmal auricular tachycardia as the result of minor gastric complaints in patients with perfectly normal hearts. Digestive disturbances in some as yet unknown manner cause abnormal impulses in the rhythm center in the auricle with the resultant production of paroxysmal auricular tachycardia. The occurrence of auricular fibrillation found momentarily in such occasional cases denotes, I believe, that the abnormal impulses have tended to race the auricles at a speed beyond that of auricular tachycardia, so that the auricles can no longer beat rhythmically, and in its place the disorderly activity implied by auricular fibrillation occurs.

Regarding fibrillation from fright and other emotional causes (Table III), I shall refer you to case VIII, in which fright seemed to be the etiologic factor.

Digitalis (Table III) may produce auricular fibrillation. I had one such case under observation several years ago. A boy with a decompensated mitral regurgitant lesion and an otherwise rhythmic heart showed fibrillation every time he was under the maximum effects of the tincture of digitalis. Polygraphic tracings left no doubt as to the type of the arhythmia. I tried the digitalis experiment several times; when the drug was discontinued fibrillation stopped and the pulse became regular at the end of a day or so; when it was again administered the auricles again fibrillated. It is interesting to note that, though the auri-

cles were fibrillating, the patient felt perfectly well, with compensation completely restored. In this case the toxic action of digitalis upon the vagus was probably responsible for the arhythmia; at the same time the contractile power of the heart—that is, its pumping power—was considerably improved by the drug. It has been shown experimentally that if the entire gastro-intestinal tract of a cat be removed, from esophagus to anus, and digitalis be injected intravenously, the cat will go through the action of emesis. In other words, the drug apparently possesses some action upon the cerebral center. Thus, the vomiting caused by digitalis may be similarly explained in patients to whom we have given too much digitalis, or who are particularly susceptible to the drug. It offers a more plausible explanation than the usual one that digitalis causes vomiting by irritating the gastric mucosa.

Referring again to Table III, I now wish to discuss the relation between toxins and fibrillation. Fibrillation occasionally occurs in pneumonia in adult and older individuals, in those with normal hearts as well as those with valvular and other cardiac disease. I presume the usual impression of pneumonic toxins which effect the heart is that they possess a destructive influence upon the cardiac muscle, valves, and coronaries. In almost every postmortem in pneumonia there is some cloudy swelling of the cardiae muscle, it is true, but it does not differ in degree or kind from that often found in other infectious fevers. In my opinion auricular fibrillation occurring during pneumonia is not due to such pathologic change, but is caused by some damage to the nervous mechanism—*i. e.*, to the neurogenic control of the heart. In what way toxins may thus act I cannot tell you. Although we use the term frequently, we possess so little knowledge about toxins and their effects on nerve structures that further discussion along these lines would be purely hypothetic. But it has been my experience (and clinical experience, after all, is important) that cases of fibrillation which occur in pneumonia in patients with previously normal hearts do not even after years show any damage to the heart as the result of the arhythmia. I do not wish to leave you with the impression that pneumonia may not

produce wide-spread damage to the myocardium and other cardiac structures. As a matter of fact I believe that this disease is often the insidious and first cause of a good deal of cardiovascular damage which shows itself in later life alone. This statement is scarcely susceptible to proof, because the process is so insidious and slow. For example, in a patient whom I saw some years ago, there was no doubt as to the correlation between a severe pneumonia contracted some years previously and the very gradual onset of cardiosclerosis. In pneumonia with fibrillation it seems difficult to conceive of severe cardiac damage which would show itself immediately after the pneumonia had run its course; in the cases I have observed I could discover no sign of cardiac disease either during fibrillation or immediately thereafter.

In concluding the remarks on fibrillation I want again to emphasize the importance of bearing in mind some such scheme as the tables which give the physiologic, clinical, and experimental causes. Always try to correlate etiology with the case in hand. In that manner you can attack the therapeutic and prognostic problems more readily and rationally. Such study will also help eliminate mistakes in the application of drugs.

STUDENT: What preparations of digitalis do you prefer; and why?

DR. NEUHOF: The action of all the digitalis bodies is alike. I prefer the tincture because it can be given in smaller doses, because of its uniform strength, and because it is fairly stable by reason of its alcohol content. Next in preference is digipuratim or digitan because it is a standardized preparation. In an emergency I prefer strophanthin for its quick effect; one ampule containing 1 c.c. is injected intravenously or intramuscularly; it should be injected slowly. It is particularly indicated at the onset of severe decompensation or when auricular fibrillation comes suddenly with signs of circulatory failure. Digalin is variable in strength, and hence is not as good as the other preparations just mentioned.

STUDENT: Does the effect of strophanthin last as long as digitalis?

Dr. Neuhof: No, it does not. Its effect lasts twelve to twenty-four hours; therefore it is necessary to follow it with digitalis. Sometimes it has a most remarkable and beneficial action within an hour or two.

Student: In auricular fibrillation is there any contra-indication to the use of strophanthin?

Dr. Neuhof: If you have given much digitalis before, do not give strophanthin.

CASE V.—AORTITIS WITH ATTACKS OF AURICULAR FIBRILLATION

M. S., male, aged fifty-two, is married and has two grown children. He gives the following history: He has never had rheumatism. Twenty-five years ago he had a severe attack of jaundice. Thereafter he suffered from pyrosis and abdominal pain. About five years ago he was awakened suddenly at night by his first "heart attack"; this consisted of a feeling of "thumping in the chest" lasting several minutes. Some years later he was operated upon for appendicitis and purulent cholecystitis. Since these operations he has had no gastric symptoms except when eating fatty food; he then had some belching and pyrosis. Seven years ago he had typhoid fever, and four years thereafter pneumonia. During the last two years the "heart attacks" are more frequent, occurring even daily. They last much longer than formerly, sometimes for hours. He has been a smoker in moderate amounts, but he does not smoke at all now. He sleeps very poorly; his sleep is often disturbed by erections, by thoughts of business, or by introspection regarding his heart. Digitalis in small doses had improved his cardiac condition somewhat. The bromids produce restful nights. He wakes up hungry and feels worse before breakfast when washing and dressing. When not annoyed by the "heart attacks" he feels well and is able to attend to business.

Examination.—The patient has given us a very intelligent and continuous story of his abdominal and cardiac complaints. The first point to determine is the nature of these "heart attacks." I was fortunate enough to examine the patient during one of the paroxysms. The heart at first beat rhythmically; then,

while the patient was sitting quietly, he said, "I am having an attack." The pulse and heart action suddenly became grossly irregular and rapid, with all the clinical characteristics of auricular fibrillation. An electrocardiogram which I immediately took confirmed the type of arhythmia. There was no dyspnea, the patient simply complained of an uncomfortable feeling of "palpitation." The attack lasted several minutes. I was able to decrease the cardiac rate slightly by sudden sharp momentary pressure upon the left and right vagus, but the irregularity continued unchecked.

At present the patient, as you see, is perfectly comfortable. He is a very well-preserved man for his years. The blood-pressure, urine, and lungs are normal. The heart and pulse are now regular. Inspection and palpation of the cardiac area reveal nothing abnormal. Upon auscultation, the first sound over the right base is rough; all the other cardiac sounds are normal. Except for the scars of previous operations the abdomen presents nothing abnormal. There is slight edema of the legs as you note by the pitting upon pressure. The orthodiascopic tracing which I here show you presents definite evidence of enlargement of the first portion of the aorta; the remainder of the cardiac outline is normal in size and contour.

To summarize: The patient many years ago suffered from painful digestive symptoms and from "heart attacks." The former were cured by operation. The latter were at first infrequent, but during the last two years they have increased in frequency and duration. Insomnia has been an added symptom, probably because the patient is worried about his attacks.

We have no means of deciding whether the "heart attacks" years ago were of the same nature as the recent ones. From the patient's description of both, the probabilities are that they are identical. The original paroxysms of auricular fibrillation—for such is the type of the present arhythmia—may have been the result of reflex excitation of the cardiac nerves, the old dyspepsia. The dyspepsia itself was due to appendicitis and cholecystitis. You gather from the history that even now the patient is sometimes awakened by abnormal hunger sensations.

Why are the paroxysms more frequent of late? The cardiac examination may offer the correct explanation. The rough first aortic sound, the dilated aorta, and the edema of the legs are probably due to aortitis with cardiac insufficiency. The irregular heart action *per se* may also have caused the edema, but the latter seems more likely a part of the composite picture of mild cardiac decompensation. The changes in the aorta are probably comparatively recent, otherwise there would not have been this long remission of the cardiac symptoms. The aortitis may have had its origin in the attack of pneumonia three years ago. Such gradual progressive changes following pneumonic infections are, I believe, by no means infrequent. They rarely appear immediately after or during the pneumonia, but are one of the late sequelæ. The pathologic changes in the aorta—possibly also involving the coronaries—can account for a recrudescence of the old attacks in more severe form. The fact that the patient feels worse upon arising and before breakfast is also of interest. I have observed similar instances in other types of heart disease. It seems due to the fact that it requires an added effort, and is a tax on the weakened cardiac reserve to carry on the circulation properly when the patient first moves about mornings. The hunger experienced in the morning may also cause reflex vasomotor disturbances which deleteriously affect circulatory stability.

Therapeutically I would first reassure the patient. There in no harm in giving him bromids at night for the insomnia. I should also advise him to take a glass of warm milk before retiring so that the stomach be not too empty mornings. He should have a glass of warm milk given to him every morning while still in bed. I should treat him intensively with digitalis for one week instead of the irregular doses he has been taking. For this purpose he should have one digitan tablet daily for one week. This would have the effect not only of helping the circulation but also of increasing the tone of the vagus. The latter is one of the effects of digitalis. You remember in this connection that I had stated that pressure on the vagus decreased the cardiac

rate during a fibrillation attack; the mechanical pressure probably acted as a stimulus to the vagus.

Later Report.—The family physician has reported to me that the patient followed the treatment outlined, and that the "heart attacks" have thus far been very infrequent and of short duration.

CASE VI.—MYOCARDITIS—AURICULAR FIBRILLATION—DECOMPENSATION. THERAPEUTIC RESULTS

M. K., male, aged fifty-five, gives the following history: He considered himself well until two years ago. He is a moderate smoker. There is no history of scarlet fever, rheumatism, or of venereal infection. Two years ago he began to cough and to have shortness of breath; later he developed epigastric pains and "palpitation" upon walking. His legs are often considerably swollen.

Examination.—You note at once the patient's orthopnea. Upon inspection of the chest you observe the diffuse irregular ventricular activity; corresponding to it the pulse is also completely irregular in force and rhythm; in other words, the patient has auricular fibrillation. The radial arteries are not thickened. Corresponding to the irregularity in force of the ventricular systoles the blood-pressure of the various beats fluctuates considerably. The majority of the beats registers a systolic blood-pressure of less than 150 mm. There is no pain on precordial palpation. Upon auscultation you hear a soft systolic murmur at the apex; there are no thrills or other abnormal sounds to be heard during systole or in the occasional long diastolic pause. The liver is moderately enlarged. There is tenderness upon pressure in the epigastrium. There are bubbling mucous râles and sibilant breathing over the entire chest. At present there is no edema of the legs. The urine contains some albumin with granular and hyaline casts. The orthodiascopic tracing reveals no enlargement of the aorta, but, as you see, the left ventricular and right auricular curves are considerably enlarged, giving the cardiac contour a somewhat rounded appearance.

It is evident that the patient is suffering from severe decom-

pensation, as shown by the dyspnea, the auricular fibrillation, and the signs of bronchial, pulmonary, and hepatic congestion. The anatomic cardiac lesion is less easy to diagnose. The only abnormal sound is the soft systolic apical murmur. Perhaps, if the heart action can be made more regular and slower by drugs, especially digitalis, we may hear other abnormal sounds not audible now. The renal condition may be the primary disease, although it is more probably the result of circulatory congestion. For the present I believe we must regard the cardiac condition as due to myocarditis for the following reasons: the absence of physical signs of an endocardial lesion, the orthodiascopic evidence of ventricular enlargement, the absence of aortic enlargement, and the absence of any rheumatic or other history which would be likely to cause an endocardial lesion.

The results of therapy in this case will practically depend upon what we can accomplish by intensive digitalis and theobromin medication during the next week or two. The patient tells us he has received digitalis, but from his account I believe in insufficient quantity. I shall prescribe the tincture of digitalis in teaspoonful doses three times daily for three days; then he will be placed for two days upon a strict Karell diet, and take theobromin sodium salicylate in 7-grain doses four times daily. If this intensive medication is followed by good results, the digitalis will be continued in smaller doses, and the theobromin and Karell days will be prescribed at more frequent intervals.

Later Examination.—This patient you saw four weeks ago, markedly decompensated and dyspneic. The therapy I then suggested has been carried out. As you can see even without a detailed examination there has been marked improvement in the patient's condition. He tells us he feels quite well and comfortable. He is able to walk without dyspnea or palpitation. The râles in the chest have almost entirely disappeared. The liver is much smaller; there is no epigastric sensitiveness. The ventricular rate is now 60 per minute; it is fairly regular in force and rhythm. Upon auscultation no murmurs are heard. The urine contains no albumin. The average systolic blood-pressure is now 160 mm.

This patient shows the brilliant result of digitalis therapy. He is now in excellent condition and may even do some light physical work. He will have to continue taking digitalis, and occasionally theobromin and a Karell diet for an indefinite time, in order to prevent a recurrence of decompensation and dyspnea. Digitalis, in the patient's present condition, may be given in 10-minim doses once daily; the theobromin and Karell diet for two days every month. In the absence of any cardiac murmurs even now, with the slow heart action, I believe our original diagnosis of myocarditis is correct.

CASES VII, VIII, IX.—TRANSIENT AURICULAR FIBRILLATION

In a previous clinic I demonstrated to you several cases of transient auricular fibrillation. I now have the opportunity of showing you 3 others.

Case VII.—Transient Auricular Fibrillation Due to Coffee.— S. K., aged thirty-five, was a heavy smoker in former years, but stopped because smoking produced precordial pains. He had influenzal pneumonia some months ago; this was not accompanied by any arhythmia. The night before I saw the patient he said that he drank two cups of very strong, almost black coffee, a very rare thing for him. He recalled that the coffee was very strong because it required an exceptional amount of sugar in order to sweeten it. One hour after drinking the coffee he felt a "fluttering around his heart"; he took his pulse and found it irregular. He had no dyspnea and slept well the entire night. He had no subjective symptoms the following day. He kept to his bed for precautionary reasons, simply because his pulse was still irregular.

Examination.—You observe that the patient is quite comfortable now, being neither dyspneic nor suffering from any distress. In fact, to judge from his laughing countenance, he considers the whole matter a joke. The highest systolic blood-pressure registered by the strongest beats is 120. This excludes hypertension. I am not going to attempt to find the average blood-pressure, a process which requires some calculation, be-

cause I consider it unnecessary in this case. You note that both pulse and heart action are completely irregular in time and rhythm, the characteristics of auricular fibrillation that I have so frequently pointed out to you. Aside from the arhythmia, there is not the slightest evidence of cardiovascular disease; there is no dyspnea, there are no murmurs, there is no precordial or epigastric sensitiveness, the liver is not enlarged, there is no edema of the legs, the lungs are normal, the urine is normal, and there is no history of rheumatic infection.

I believe that the auricular fibrillation is due solely to an overdose of coffee and not to any organic heart disease. I have never seen or heard of a similar case due to coffee poisoning, but the history is so clear and unmistakable that I think this diagnosis is justifiable. The further progress of this case will probably substantiate or upset the diagnosis. If the arhythmia be of functional origin and due to an overdose of coffee, the auricular fibrillation should disappear within a day or so, that is, after the caffein has been eliminated from the system. I do not believe any medication is necessary at present.

Examination Next Day.—You observe, gentlemen, that the patient's pulse and heart action are regular now and that all the heart sounds are normal. He feels perfectly well. The disappearance of the arhythmia justifies our original diagnosis I believe, namely, that it was caused by an overdose of coffee.

Coffee is known to occasionally cause extrasystoles, probably by increasing excitability of the cardiac nerves. Although the mechanism of their actions may be entirely different, caffein seems thus to have an effect upon the heart somewhat similar to that of digitalis, in that both produce extrasystoles and auricular fibrillation in susceptible individuals.

Case VIII.—Auricular Fibrillation From Fright.—Mrs. D., aged seventy, had an attack of influenza some months ago; otherwise she does not recall any recent illness. Yesterday she suddenly became dizzy and fell. This frightened her very much. Soon thereafter her heart began to "palpitate"; there has been "palpitation" ever since. I can get no further details from her.

Examination.—You observe, gentlemen, that although the patient looks her years, she has not the thickened radial or temporal arteries common in the old. Nor is she very dyspneic. Her heart and pulse action are typical of auricular fibrillation: both are completely irregular in force and rhythm. The heart sounds, the urine, and the lungs are normal. There is no edema of the legs, there is no precordial or epigastric sensitiveness. The heart is apparently not enlarged to percussion.

The question now arises, What is the cause of the sudden onset of auricular fibrillation? Two main probabilities suggest themselves: either this patient may have had a coronary infarct, an accident not so very infrequent in older people and not uncommonly associated with auricular fibrillation; or sudden fright following the dizzy spell and fall may have caused the arhythmia by some acute circulatory disturbance in the brain, possibly in the neighborhood of the cardio-inhibitory center. I am inclined to the latter hypothesis despite the greater chances of coronary disease in a person of advanced age; indeed, the original attack of giddiness may even have been of cardiac origin. In favor of a functional cause—fright—is the absence of dyspnea and of gastric disturbance, and the fact that the arhythmia immediately followed the fall. I shall prescribe digipuratum tablets, one three times daily. We shall re-examine the patient in a day or two; perhaps the further course of the case will indicate the correct diagnosis.

Examination Two Days Later.—This patient, you recall, I presented as a case of transient auricular fibrillation. You notice now that the pulse and heart actions are normal. There are no murmurs. The patient is quite comfortable. I shall discharge her and let her follow her usual occupation.

I believe that the cause of the auricular fibrillation was fright, for I do not think that digitalis would so quickly have cleared up the arhythmia if it had been due to a coronary infarct. When the latter interferes sufficiently with the intracardiac circulation to produce auricular fibrillation it would almost of necessity cause other cardiac symptoms such as pulmonary edema and precordial pains.

Assuming that the arhythmia is of functional and not of organic cardiovascular origin, let us theorize for a moment regarding the possible mechanism which induced the auricular fibrillation. One may, for example, hypotheticate that the fall itself, causing a sudden change of blood-pressure, produced sufficient disturbance in the vasomotor tone and in the cardio-inhibitory center to have induced the arhythmia. Or, subsequent to the fall, there was vasomotor instability, thus upsetting the usual control of this center. Even giddiness *per se* may conceivably reflexly alter the vasomotor tone and thus produce cardiac irregularity. I realize, of course, that we are heaping up theoretic assumptions with a meager substratum of facts. But it is a rather common clinical experience that sudden fright, for example, produces severe tachycardia and extrasystoles, and I see no reason why it may not also cause auricular fibrillation in exceptional instances. The more I observe and study arhythmias, the more I am impressed by the fact that the most bizarre as well as the most common types can follow functional derangements. I have even observed a case of heart-block of functional origin. I was able to follow that patient to autopsy, for he was killed in an elevator accident. Careful macroscopic examination of the heart showed no lesion in the auriculoventricular conduction system nor in any other part of the heart.

Case IX.—Transient Auricular Fibrillation—Permanent Hypertension.—A. K., married, aged fifty-eight, had been a moderate smoker. He had gonorrhea many years ago. He has not had any recent acute diseases. He had always been athletic. Except for cardiac "attacks," of which this is the fourth, he had never had any cardiac symptoms. The first attack occurred four years ago. The patient believes it was the result of too much swimming. The second he believed followed too much smoking.

For several weeks past he has been worrying over financial matters. One night he suddenly noticed that his heart beat very irregularly, at which time be became dyspneic. Prior to this, even though working hard, he never was short of breath.

Examination.—This is the fourth day, the patient tells us,

that his pulse and heart action have been irregular. You observe that he is not dyspneic now, although he is lying rather flat. Both heart and pulse are irregular in time and rhythm, typical of auricular fibrillation. If you will listen to the heart you will find that the second sound over the right base is somewhat accentuated; the other cardiac sounds are normal. There is no pain on precordial pressure nor does the patient suffer from any subjective precordial discomfort. The systolic blood-pressure of most of the effective beats ranges between 160 and 170. The liver is not palpable. The urine is normal. The Wassermann examination of the blood is negative. There is no edema of the legs. The eye-grounds, as reported by the ophthalmologist, show no evidence of arteriosclerosis. The orthodiascopic tracing being passed around shows moderate enlargement of the first portion and arch of the aorta. The remainder of the cardiac outline is normal in size and form; in other words, there is no evidence of ventricular hypertrophy.

To summarize: This patient has auricular fibrillation now; the other past "attacks" may also have been examples of the same arhythmia. The definite cardiovascular abnormalities that the patient presents are an accentuated second aortic sound, an enlarged aorta as demonstrated by the *x*-ray, and moderate hypertension. I believe that the aortitis is of the slowly progressive type, for there would otherwise not be such long remissions of cardiac symptoms. You see the patient looks very robust for a man of his years, and even now, despite fibrillation, he does not feel ill. You may recall that I have already shown you one or two examples of aged individuals with very much enlarged aortas who were suffering from very few cardiac symptoms. Our patient seems to belong to that group. I believe that financial worry has much to do with the onset of this last pulse irregularity. As I picture the case it seems to me that the neurotic element may have been a factor in causing the arhythmia and even the hypertension. I shall place the patient upon digitan for several days; for three days I shall give him two tablets daily, and then for six days one daily. He is also to receive 15 grains of the triple bromids every night. I believe

the arhythmia will disappear soon and that the blood-pressure will become normal. I shall report to you the further progress of the case at some future time.

Report Four Months Later.—The patient took the medication I had authorized. I then sent him to the seashore for several weeks. I have seen him often during the intervening four months. One week after the examination the pulse became normal and has remained so. The blood-pressure varies between 190 and 200 systolic, and from 130 to 100 diastolic. Our examination of the phenolsulphonephthalein output for two hours was 40 per cent. The patient is again active, but is not rushing about quite as much as formerly. His only complaint has been slight dyspnea upon walking up-stairs and slight palpitation. These symptoms have no correllation with the height of the systolic or diastolic pressures. From all present indications, the hypertension seems to be permanent. Whether it antedated the time we first examined him we have no means of ascertaining because the patient had not had his blood-pressure taken for many years.

I scarcely believe that a latent interstitial nephritis plays an important rôle in the hypertension of this patient because none of the usual earmarks of nephritis are present. Neither the dyspnea, pallor, anemia, gastric or precordial symptoms, eye-ground changes, nor low phthalein output is present. On the other hand, I do not wish to diagnose this case as one of so-called functional hyperpiesis, for the enlarged aorta is distinct evidence of some organic arterial change. Nor can the patient for the present be placed among the benign arteriosclerotic group, because the cardiac symptoms are too prominent. Indeed, an infarct in one of the smaller branches of the coronary artery may be the underlying cause of the arhythmia. For the present, therefore, this case must stand as one in whom the origin of the attacks of auricular fibrillation cannot be determined.

CLINIC OF DR. WALTER F. MACKLIN

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THE PREVALENCE OF HETEROPHORIA AND ITS INFLUENCE UPON GENERAL HEALTH

I WISH to present for your consideration a group of cases having heterophoria (extra-ocular muscle imbalance) as their origin. These cases exhibit, in addition to the local eye manifestations, certain general symptoms. These may closely simulate definite gastric or nervous diseases, or may be indefinite and variable in character, thus, in either case, leading to an erroneous diagnosis and treatment which fails to relieve or gives, at best, but a temporary respite. As a natural consequence these sufferers try one physician after another in the hope of a cure until the true cause is discovered and corrected.

This particular eye condition is, therefore, of special interest and importance to the general physician and is worthy of his serious consideration and study. We shall not go into a technical analysis of the condition itself or consider it, at present, from the viewpoint of the specialist, but rather from that of the physician called in to see such a case. What does he find, and what points should make him suspect the presence of heterophoria?

Speaking first in general terms, these cases may show purely stomach symptoms, purely nervous symptoms, or a combination in varying degree. The onset is usually very mild, with slow progress, and will probably have been running along for some time before the physician is consulted. There will ordinarily have been several milder and shorter attacks previous to the one in which advice is sought. Sometimes a history of a chronic indigestion extending over a period of a couple of years or more will be given. In others a similar history of nervous disturb-

ances, lassitude, dizziness, headaches, etc. It will often happen that these patients have had their eyes examined and are wearing glasses, for the mere correction of errors of refraction will not, as a rule, suffice. This is especially true of those fitted by the optometrist or refracting optician, but is also, unfortunately, true at times of the legitimate specialist who overlooks this highly important field of his work.

I have made a special study of muscular anomalies of the eye, and so perhaps get a larger number of these cases than I otherwise would, but I doubt if the difference is very marked and so believe we can accept some statistics of mine as fairly representative. Out of 2669 consecutive cases of refraction in my private practice that I have tabulated, 654, or 24½ per cent., showed muscle anomalies of two degrees or more of esophoria or exophoria, or one degree or more of hyperphoria, or a combination of these, or had esotropia or exotropia. Of these 654 cases, treatment resulted in a complete cure in 80 per cent. and improvement in 17 per cent. more, while 3 per cent. remained the same or grew worse. A number were not treated by me because they had come for diagnosis and lived at a great distance and could not take the time, or had other reasons for not taking the treatment.

Of those who were merely improved, and those who remained the same or grew worse, almost all gave up treatment before a fair trial was given. I believe it is safe to say that, with proper co-operation on the part of the patient, a cure can be obtained in about 98 per cent. of the cases.

In this group of 654 cases there were:

170 of esophoria,
96 of exophoria,
152 of left hyperphoria,
44 of right hyperphoria,
67 of esophoria and left hyperphoria,
39 of esophoria and right hyperphoria,
24 of exophoria and left hyperphoria,
19 of exophoria and right hyperphoria,
29 of esotropia,
14 of exotropia.

General systemic disturbances, of course, are not nearly so common or severe in the cases of squint as they are in the phorias, and especially in hyperphoria.

Let us now consider more in detail the symptom-complex of heterophoria.

Eye Symptoms.—There may be impaired vision unless correcting lenses are worn. If they are worn, vision will be normal except for diplopia, or double vision, which may be present at times, and will be more common when the eyes are fatigued. It will also be more apt to be present when the patient is in poor physical condition or overtired. The diplopia may be noted only in distant vision, only in near vision, or for both far and near. The eyes may ache, and usually tire easily, especially after near use. There may be irritation of the conjunctiva, with some congestion. In the highly nervous cases various and unusual symptoms and sensations may be complained of—fading image or everything appearing dark before one eye, etc. Eye symptoms may be absent.

General Symptoms.—The attempt to avoid diplopia may result in a peculiar attitude or tilt of the head. There may be spasm of the facial muscles. The most common symptom is headache. This may be supra-orbital, frontal, temporal, or occipital. Dizziness is very common, and varies from a slight manifestation to the more severe degrees in which the patient will stagger, or fall, or lose consciousness, leading to marked nervousness and loss of self-confidence. In one of my cases the diagnosis of true epilepsy had been made, the patient having from one to four epileptiform seizures daily. This man became quite free from these manifestations once his muscle balance was restored, and has remained cured now for more than ten years.

Indigestion is another very common symptom, and varies in degree and character. In some it is slight, in others it becomes a very serious factor, and in these cases is generally regarded, for some time, as the real seat of trouble. Many go through prolonged treatment for this condition with only temporary relief, and come to regard themselves as chronic dyspeptics, and become

resigned to a restricted diet. The others have periodic attacks and usually attribute them to some indiscretion in diet.

Car sickness is fairly common, and may be severe enough to lead to nausea and even vomiting. It is not uncommon to find those who cannot go through the day's work without unusual fatigue and lassitude, making life a drudgery; or young women who cannot spend an evening at the theatre, or a dance, without having to spend the next day in bed with a severe headache and probably indigestion.

It is not surprising then that this condition may lead the patient to believe that he has some serious organic lesion, to fear cardiac involvement, and to go below par and to become depressed and neurasthenic, or that the physician should make an error in diagnosis.

Let us now pass on to a brief consideration of heterophoria itself. The phorias show no manifest squint, and are only detected and determined by special tests, *i. e.*, the screen, the parallax, the Maddox rod, and the phorometer. In esophoria there is convergence excess or divergence insufficiency, or a combination of these. In exophoria there is divergence excess. convergence insufficiency, or a combination of these; in hyperphoria there is an overstrong rectus superior or inferior in one eye or a weak rectus superior or inferior in the other, or a combination of these. There will be a further combining of these conditions when there is a mixture of esophoria or exophoria with hyperphoria. The condition of perfect muscle balance for far and near is known as orthophoria.

Binocular single vision in heterophoria is maintained by special nervous and muscular effort, and this effort tends to use up the reserve nerve and muscle energy. It is a constant drain and, in proportion to its extent and duration, will naturally manifest itself in the symptoms I have mentioned. In the physically strong there will be less disturbance than in the feeble, and the disturbance will increase with fatigue.

How shall we treat these patients? One has the choice of: (1) Prescribing prisms to be worn in combination with the regular correction, which simply relieves the symptoms, but does not

cure the condition; they are more useful in hyperphoria than in esophoria or exophoria. (2) Operation—performing a partial or complete tenotomy, single or double, a muscular or capsular advancement, or some combination of these. (3) Using the stereoscope, with special cards, or the Worth amblyoscope. The latter is of special value where the fusion faculty is undeveloped or faulty. (4) Prism exercises used to develop the weak muscle or muscles to the point necessary to establish an exact balance. (5) Stimulation by the electric current applied to the weak muscle—used as an adjunct to the exercise.

The exercise is always my first choice, and usually succeeds admirably, and has the great advantage of accuracy, permanency, and logic in its favor, besides being much more agreeable to the patient than the idea of an operation. In cases of excessive degree and long standing, in which exercise has failed to give results, operation should be resorted to, as in those cases coming from great distances with too limited time to remain for treatment.

I give the exercises with the Risley rotary prism on the phoro-optometer with correcting lenses worn and a lighted candle at a distance of 20 feet from the patient. There is a dark, dull background for the candle. There are no other lights within view of the patient to confuse him. The Risley prism gives a prism range from 0 to 30 degrees, and by its means the muscle can be made to carry a graded load in proportion to its power. At first this power will be small, but development comes with the exercises, really graduated weight lifting, until orthophoria is established. It can be used on the horizontal axis to develop the internal or external recti, and on the vertical axis to develop the superior or inferior recti muscles.

Where there is considerable lack of tone in the muscles and they fail to respond to the exercise, I use electric stimulation—usually a combined galvanic and faradic current with mechanical interruptions of 130 to the minute. I take this current from a wall cabinet, making applications to the weak muscles with one electrode, the patient holding the other electrode in one hand. This is a valuable adjunct to the treatment.

Hyperphoria may be treated by wearing, combined with the regular correction, a prism partially correcting the error, then reducing its strength as the degree of hyperphoria decreases. For example, in a case of left hyperphoria of 3 degrees in a patient having a manifest hyperopia of 0.75 D., the correction would be O. D. plus 0.75 D. Sph. $\bigcirc$ 2 degree Prism Base Up. O. S. plus 0.75 D. Sph. When the hyperphoria is reduced to or nearly to 2 degrees, cut the prism in the right lens to 1 degree or 1½ degrees, finally removing it entirely when sufficient reduction in the hyperphoria has taken place. The use of prisms in correcting lenses in horizontal deviations is not wise, except in cases that run above 8 degrees, and then should not correct more of the error than is in excess of 6 degrees, always depending upon exercise to correct the trouble, cutting down and removing the prism as soon as possible. For example, in a case of esophoria of 9 degrees that is very resistant to exercise, one may order a 1½ degree prism, base out, in each lens and keep on with the exercises, removing the prisms when the esophoria has decreased.

In giving the exercise the patient looks at the candle with both eyes open, correcting lenses worn. The Risley prism is set at 0 degree, and the patient sees a single light. Now, turn the prism adjustment until he sees double and immediately reduce the strength until he gets single vision again. Repeat this several times and then give a moment's rest. Continue this until the muscle begins to show fatigue, then stop entirely for the day. As a rule, three treatments weekly will give the best results, but this varies, of course, with individual cases. Some patients do best when treated every day; others when treated every third day. Longer intervals will rarely give any degree of progress.

In the great majority of cases, then, it is best to give three treatments weekly, and we may expect a cure in anywhere from three weeks to three or four months. Old, obstinate, and severe cases may require a much longer period, but these are exceptional. All associated troubles should be corrected, especially nose, throat, and teeth.

In conclusion let me say that we find here patients who really

suffer, who are wretchedly uncomfortable, highly nervous, often distinctly below par, and who are apt to be regarded as pure neurasthenics, since it is so difficult to put one's finger on any real cause for their symptoms, and because these symptoms are apt, in many cases, to vary and sometimes to be vague and dissociated. Some fear to go out alone lest they fall in the street, or lose consciousness; others lose their positions and the confidence of themselves and their friends. Many others go on about their daily routine, but without snap or enjoyment, everything they do being an effort. It is truly remarkable what a metamorphosis takes place when the real cause of trouble is discovered and removed.

It should be remembered that this condition occurs also in children, and that many a nervous child, backward in school work and with various nervous disturbances, owes its whole trouble to heterophoria.

CLINIC OF DR. MAX KAHN

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CLINICAL SIGNIFICANCE OF ACIDOSIS

EVERY individual cell and all aggregation of cells during their life are constantly building up and breaking down matter which is thrown off into the fluids and juices which bathe the tissues. The mechanics and chemistry of these reactions are arranged with an exact nicety, with a simplicity, and yet with an intricacy of interrelationship that causes one to marvel. The health, the very life of the cell, or tissue, or animal depends upon the proper exchange of waste and nutritive products, and upon the proper removal, neutralization, or detoxication of the effete substances. Death, local or general, immediately supervenes should the waste products be allowed to accumulate indefinitely, or should their influences not be counteracted.

The animal organism is a very complicated mechanism. It is a factory into which raw material is constantly brought, is subjected to certain furnace actions, the smoke being constantly exhausted through the chimneys, and the waste matter disposed of through the various sewerage systems. Obstruct the chimneys and the fires in the furnaces will smoulder until, finally, they will be extinguished. Interfere with the proper sewer circulation, and the factory must postpone work for repairs or else cease producing entirely.

The question of acidosis includes a complete understanding of the exact regulation of the composition of body fluids, and of the mechanics and chemistry of the excretory channels of the body. The tissues of the body are bathed by blood and by lymph of remarkably uniform composition. In these fluids are dissolved many substances which tend to make these fluids

either more alkaline or more acid. We must, therefore, pay some attention to these alkali- or acid-forming substances before we proceed further with our discussion.

When a substance such as hydrochloric acid or potassium hydroxid is dissolved in water it is found that it dissociates or splits into two parts (which carry positive or negative electric charges) called ions. In the case of hydrochloric acid the ions will be H and Cl, and in the case of potassium hydroxid the ions will be K and OH. All known acids dissociate with the liberation of the H ion, and the most accurate measure of the acidity of a solution depends upon the determination of the amount of H ion present. On the other hand, the OH ion is a measure of the alkalinity of a solution.

McCleod writes: "We have learned two fundamental principles, namely, that the standard of perfect neutrality must be where H′ and OH′ ions exactly balance each other, and that the true acidity of a solution will be represented by the excess of free H′ ions over OH′ ions, that is, by the H′ ion concentration. But we can go further, for not only may the acidity be expressed in terms of H′ ion concentration but also the alkalinity. Why should this be? It is clear that the most strictly neutral solution must be pure water in which H′ and OH′ ions are exactly counterbalanced. Nearly all of the H′ and OH′ are combined in an undissociable molecule water, but not all, for even in the purest water a slight degree of dissociation occurs, giving us, therefore, H′ and OH′ ions. When the concentration of the two ions are multiplied together the product is 1.2×10^{-14}, which means that there are 1.2 gram molecule of hydrogen (or its equivalent) present in 10,000,000,000,000 liters. Since the concentration of H′ and OH′ ions are equal, the H′ ion must, therefore, be 1.2×10^{-7}, which means that this ion is present so as to form a 0.000,000,12 N solution, that is, 1.2 gram molecule of H′ ion in 10,000,000 liters.

"When some acid is added to water the concentration of H′ ions, of course, rises, and this is the fundamental point to bear in mind, the concentration of OH′ ions correspondingly falls, so that, as in pure water, the product of the two concentra-

tions is again 1.2×10^{-14}. However acid or alkaline a solution must be, the product of the H′ and OH′ ions is always the same. Clearly then we may express the reaction even of alkaline solutions in terms of the H′ ion concentration. Whenever this is greater than 1.2×10^{-7} the reaction is acid, but when it is less than 1.2×10^{-7} the reaction is alkaline."

The fluids that bathe the body are remarkably constant in the H′ ion concentration. Should, experimentally, an attempt be made to increase the H′ ion concentration by feeding the animal acid substances or by injecting acids intravenously, it will be found that it needs much more acid to increase the H′ ion concentration of blood than if these substances were added to water. There must, therefore, be something present in the blood and lymph (which is not present in water) which resists the influence of these acids or which absorbs or soaks up these H′ ions as quickly as they are produced. These resisting or soaking up substances are the so-called "buffer" or "tampon" substances of the blood.

The first tampon substance met by the acid when injected into the blood is the sodium bicarbonate of the blood plasma. With it the acid reacts to liberate carbon dioxid and form a salt, thus:

$$NaHCO_3 + HA \text{ (any acid)} = CO_2 + H_2O + NaA \text{ (salt)}.$$

This is the first line of defense of the body against accumulation of H′ ions in the blood. Now, it has been found that in normal individuals the molecular ratio of carbonic acid to sodium bicarbonate in the blood plasma is a good measure of the H′ ion concentration of the plasma. This ratio is 1 : 20, and acidosis can be defined as any condition in which the ratio 1 : 20 is increased, that is, when the carbonic acid is increased or the sodium bicarbonate is decreased so that the resulting fraction shall be greater than $\frac{1}{20}$.

The second line of defense is the phosphates of the red blood-cells which act as powerful tampon substances, according to the reaction

$$Na_2HPO_4 + HA = NaH_2PO_4 + NaA.$$

Proteins also serve as tampons and may be considered another regulating factor.

Now what happens to the carbon dioxid produced by the interaction of an acid and the bicarbonate? It is understood that if the carbonic acid should constantly accumulate in the system the ratio $H_2CO_3 : NaHCO_3$ would be markedly increased, and a state of acidosis would be present. The lungs ventilate the carbon dioxid of the blood, and the gas is expelled so as to keep the H′ ion concentration level.

But one must remember that the carbonic acid is produced at the expense of the sodium bicarbonate, and is, therefore, a measure of the sodium bicarbonate present. Another thing one must remember is that the carbon dioxid of the alveolar air is a direct measure of the available sodium bicarbonate in the blood. As McCleod expresses it, "Since the H′ ion concentration remains constant in the blood the ratio of carbonic acid to sodium bicarbonate must also remain at its normal value of $\frac{1}{20}$, and, therefore, if sodium bicarbonate declines, the carbonic acid must decline proportionately, and since this diffuses as carbon dioxid in the alveolar air, the percentage of this gas in the alveolar air must be proportional to the degree to which foreign acids can be added to the blood without perceptibly changing the H′ ion concentration; in other words, it must be proportional to the reserve alkalinity."

What would cause an increase of the acid concentration in the animal system? The answer is quite apparent if we again compare the body to a factory. What will cause an increased accumulation of waste matter in the factory? The answer, of course, is the continued intake of working material with an obstruction in the channels of outflow of the débris. That is, if the ventilating system is obstructed, and if the sewerage is deficient, and if the factory is still running, the quarters will be made uninhabitable. The causes, therefore, of acidosis are (to enumerate them with subsequent discussion) as follows:

1. Intake of excess acids, either in the food or due to intoxication with acids, or experimentally by intravenous or parenteral administration.

2. Continued depletion of alkalies from the body, either due to a deficiency in intake or due to an excessive excretion, as in diarrhea, etc.
3. Obstruction to the body ventilation, with the resulting retention of carbon dioxid in the blood; in other words, in asphyxial states.
4. Increased catabolism in the body with liberation of excess quantities of acids, as in infections, cachexial states, fevers, etc.
5. Obstruction of the proper excretory channels of the body, either of the intestines, kidneys, skin, etc., that is, in conditions of obstipation, nephritis, etc.
6. Excess production of acid in the alimentary canal with the absorption of these acids in the blood, as in intestinal putrefaction.
7. Incomplete oxidation of carbohydrates with the formation of lactic acid, as in severe muscular exertion, etc.
8. Hepatic functional inefficiency.
9. Disturbances in the carbohydrate-fat metabolism with the resultant production of ketosis.

1. It is, of course, obvious that the constant and excessive administration of acids either enterally or parenterally will ultimately break down the tampon protective mechanism of the organism, and the H′ ion concentration will gradually increase, until finally death of the animal results. Such an eventuality is met with in experimental acid intoxications when an animal is poisoned by such substances as oxalic, citric or tartaric acids, or any of the inorganic acids, or when a human being commits suicide with one of these acids. It is to be borne in mind, however, that other factors besides the direct effect on the H′ ion concentration add to the symptoms of the intoxication. The irritative lesions induced by these substances result in pathologic changes in the various organs of the body, and thus, indirectly, increases the acidosis; for example, due to a nephritis set up by the acid, there is a secondary influence exerted tending to increase the acidosis. It is, it seems, impossible to produce a simple and fatal increase in the H′ ion concentration of the blood without

at the same time inducing secondary influencing factors to complicate the picture.

2. The continuous depletion of alkalies from the body will eventually cause a lowering of the sodium bicarbonate of the blood plasma and thus disturb the ratio of carbonic acid to the sodium bicarbonate with the induction of acidosis. Such a depletion is to be observed in the summer diarrheas of infants, where the little patients are being constantly drained by the bowel of the alkalies due to some intestinal infection. This cholera infantum as well as the true cholera and other diarrhea-inducing diseases, such as dysentery, typhoid fever, etc., cause dreadful degrees of acid intoxication due primarily to this constant loss of alkalies by means of the bowels, and, secondarily, to causes which will be discussed hereafter.

When animals are fed on diets poor in ash, or when human beings are forced to subsist upon a diet with a very low mineral content, a condition will ultimately be set up similar to the one pointed out above, *i. e.*, an acidosis will gradually arise due to a lowering of the sodium bicarbonate content of the blood plasma. In children, due to an insufficiency in the alkali intake, there may develop a condition of acidosis which manifests itself in the cyclic vomiting of infancy.

3. The ventilation of carbon dioxid by means of the lungs is regulated by the carbon dioxid of the blood through its effect on the respiratory center. In conditions of improper pulmonary ventilation asphyxial states may result which prevent the loss of carbon dioxid from the blood plasma with consequent increase in the numerator of the carbonic acid-sodium bicarbonate fraction. This will result in acidosis.

4. In such pathologic states of the body when the protein catabolism is especially marked with the resultant liberation of many acid-split products, as, for example, in the fevers, in the acute and chronic infections, in conditions of malignant neoplasms with superimposed cachexia, an accumulation of such acids will eventuate in general acidosis of the organism. This is the acidosis that one meets in the latter stages of such acute infections as

typhoid fever, in the cachexia of carcinoma, in the last stages of tuberculosis, etc.

5. Disturbances in the proper and sufficient removal of waste matter from the animal economy will lower gradually the alkali reserve of the blood. This may advance to a very severe degree. In nephritis, for example, the continual retention of the waste products of protein destruction may result in a fatal grade of intoxication, unless the other excretory channels take upon themselves the duties of the non-functioning, or poorly functioning, renal apparatus.

Similar states of acidosis will supervene in conditions of intestinal obstipation, or in states of disease of the skin, when there is interference with the excretory function of these organs.

6. In certain putrefactive states of the alimentary canal an excess quantity of acids is produced with the consequent absorption into the blood. Such fermentative processes may be either of the carbohydrate fermentation type or of the protein putrefaction type. These absorbed acids have, of course, the usual influence on the alkali reserve of the blood.

7. Acidosis may be caused by severe muscular exertion—by fatigue—due to improper oxidation of carbohydrates with the formation of the oxypropionic acids. The absorption of these acids into the system will cause a change in the carbonic-acid-sodium bicarbonate ratio.

8. Disturbances in the functional capacity of the liver may give rise to acidosis. The derangement of the detoxication and neutralization mechanism of the hepatic tissue will cause an accumulation of acids in the blood. In toxemia of pregnancy of the hepatic type, in acute yellow atrophy of the liver, in phosphorus-poisoning, in severe degrees of hepatic cirrhosis this acidosis may be fatal. It is, of course, to be remembered that in these conditions the concomitant disturbances in the various other organs—in the kidneys, etc.—will markedly add to the acidosis.

9. In certain conditions of the disturbances of the metabolism of fats and carbohydrates a condition of acidosis is estab-

lished characterized by the fact that the blood is rich in ketonic acids of a certain type. To this condition the special name of *ketosis* has been applied.

The causative factors of this condition of ketosis are:

(*a*) Starvation.

(*b*) Toxic effect of lipin-solvent anesthetics.

(*c*) Disturbances in the metabolism of carbohydrates—diabetes.

In the catabolism of fats (under normal conditions, that is, in the presence of proper carbohydrate oxidation) there is a rapid breakdown of the fatty acid radical to the four-carbon acid, *i. e.*, to butyric acid:

$$\begin{array}{lcl} CH_2\text{-}OOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R & & COOH \\ \cdot & & \cdot \\ CH\text{-}OOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R & \longrightarrow & CH_2 \\ \cdot & & \cdot \\ CH_2\text{-}OOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R & & CH_2 \\ & & \cdot \\ & & CH_3 \end{array}$$

The butyric acid is then rapidly catabolized to carbon dioxid and water.

This process is, however, markedly disturbed in states of deficient carbohydrate oxidation. In the latter circumstance the fats are primarily broken down to butyric acid, as in the normal condition, but in the absence of the heat of carbohydrate consumption the further decomposition of the butyric acid proceeds very slowly. The butyric acid under these conditions is decomposed first to beta-oxybutyric acid, and then to aceto-acetic (or diacetic) acid. The further decomposition to acetone takes place very largely in the urine itself:

$$\begin{array}{lclclcl} COOH & & COOH & & COOH & & \\ \cdot & & \cdot & & \cdot & & \\ CH_2 & & CH_2 & & CH_2 & & CH_3 \\ \cdot & \rightarrow & \cdot & \rightarrow & \cdot & \rightarrow & \cdot \\ CH_2 & & CHOH & & CO & & CO \\ \cdot & & \cdot & & \cdot & & \cdot \\ CH_3 & & CH_3 & & CH_3 & & CH_3 \\ \mathrm{I} & & \mathrm{II} & & \mathrm{III} & & \mathrm{IV} \end{array}$$

I. Butyric acid.
II. Beta-oxybutyric acid.
III. Aceto-acetic acid.
IV. Acetone.

Rosenfeld has said that fats burn only in the fires of carbohydrate, but this is not quite right, inasmuch as only the breakdown of the lowest stages of fat decomposition, that is to say, the acetone substances, depends upon the catabolism of the carbohydrates.

How does the fat decompose to butyric acid? Of the two components of fat, only the fatty acids yield the ketone substances. The glycerin portion of the fat molecule is antiketogenic in nature. "By investigations performed either with living beings in a state of acidosis or with the transfused dog's liver, it has been established that fatty acids are broken down by a repeated splitting off of two carbon atoms. The first step is the formation of the beta-oxy acid, which is then transformed to the beta-keto acid:

	COOH		COOH		COOH
(a)	CH_2		CH_2		CH_2
(b)	CH_2	→	CHOH	→	CO
	CH_2		:		:
	:		:		:
	:		:		:
	R		beta-oxy acid.		beta-keto acid.

The transformation requires a twofold oxidation at the beta-carbon atom. Contrary to what happens in the lungs with aceto-acetic adid, a splitting off of the carboxyl group and the formation of a true ketone generally does not take place in the metabolism; instead we find a simultaneous splitting off of the carboxyl group and of the alpha-carbon atom, thus yielding a new fatty acid lower by two carbon atoms" (Magnus-Levy). Embden has found that only fatty acids of an even number of carbon atoms will yield aceto-acetic acid in the transfused dog's liver. In this way from stearic acid (C_{18}) palmitic acid (C_{16}) is formed; from this an acid with 14, 12, 10, or 8 carbon atoms is derived. Then caproic acid (C_6) and, finally, butyric and oxybutyric acids are formed. The relative figures are as follows:

	Molecular weight.	Relation of molecular weight.	Per cent. yield of oxybutyric acid from 100 grams.
C_{18}	284	100.0	36.5
C_{16}	256	90.0	40.0
C_{14}	228	80.0	46.0
C_{12}	200	70.5	52.0
C_{10}	172	61.0	60.0
C_{8}	144	51.0	72.0
C_{6}	116	41.0	90.0
C_{4}	88	1.0	118.0
Oxybutyric acid	104	36.5	

It must be remembered that under certain conditions proteins also yield the acetone substances. It has been demonstrated that the amino-acids derived from proteins, leucin, tyrosin, and phenylalanin are producers of the ketone substances, while valin, glutaminic acid, aspartic acid, alanin, etc., are not.

The following methods may be used in the determination of the presence and the degree of acidosis:

1. Quantitative acidity of urine.
2. Ammonia determination in the twenty-four-hour urine collection.
3. Formol titration of urine.
4. The quantity of sodium bicarbonate necessary to be administered by mouth to the patient to render urine alkaline.
5. The carbon dioxid content of the alveolar air.
6. The carbon dioxid tension of the alveolar air.
7. The carbon dioxid combining power of the blood plasma.
8. The quantitative determination of the ketonic substances in the blood and urine.
9. The H′ ion concentration of the blood.
10. Determination of the alkali reserve of the blood.

The directions for the determination of these substances may be found in Hawk's "Practical Physiological Chemistry," latest edition.

It is always essential to combat this acidosis whenever met with, in the clinic or at the bedside. The significance—so

far as prognosis and therapy go—of the acidosis varies, depending upon the type of acidosis, the causative factor, and the degree of H′ ion concentration. By an actual measurement of the grade of acid intoxication one can classify the cases into the mild, the moderate, and the severe stages of such intoxication. It is always incumbent upon the physician to prevent the increase of concentration of acid in the blood, and to neutralize or stimulate the excretion and prevent the formation of any new acid radicals in the animal economy.

The methods that lend themselves clinically to the determination of the degree of acidosis and are not time consuming are the analysis of the alveolar air (Fridericia, Marriott), the examination of the blood plasma combining power with carbon dioxid (Van Slyke), and the measurement of the ammonia excretion in the urine. Very low figures by the Fridericia, Marriott, or Van Slyke methods, or high ammonia figures by the Henriques-Sörensen method, are danger signals that it would be well for the physician to heed. Figures under 4 per cent. by the Fridericia apparatus, or lower than 20 mm. by the Marriott instrument, or less than 40 per cent. by the Van Slyke procedure are indeed indicative of a severe degree of acidosis.

What is the treatment of acidosis? This may be discussed under the following headings:

1. Preventive.
2. Treatment of the causative condition.
3. Increasing the alkali reserve of the blood.
4. Stimulating the excretion of acids.
5. Treatment of ketosis.

1. In acidosis, particularly, the ounce of prevention is of greater value than the pound of treatment. The patient should be instructed to keep his bowels open. Occasional doses of saline or systematic lubrication of the intestines with some paraffin oil may do much to prevent the retention and absorption of toxic acid radicals. Frequently high colonic irrigation may be beneficial.

It is advisable to recommend the drinking of much water.

A glass of cold or hot water taken hourly may serve to wash out quite a lot of the effete material from the body.

The diet has to be carefully regulated. In infants and children the proper care of the food intake will prevent acidosis and its manifestations—cyclic vomiting, recurrent bilious attacks, sick headaches, or migraine. Eustace Smith believed that intestinal carbohydrate fermentation is the cause of acidosis of infancy. Holt also suggests that in the intervals between attacks all sugars and sweets be excluded from the diet. According to Pritchard, however, the cause of this acidosis is the overfeeding of their children by the overfond parents. It has been long ago said by an English writer that "good diet and wisdom best comforteth man." This is quite axiomatic. Good diet keeps no company with folly. Break the mandates of good diet and a train of evils will result.

Sherman gives the following tables of foods in which the acid- or base-forming elements predominate:

FOOD IN WHICH ACID-FORMING ELEMENTS PREDOMINATE

	Estimated excess acid-forming elements to c.c Normal acid per 100 calories.
Beef, free from visible fat	10.0
Eggs	9.0
Round steak	6.7
Oatmeal	3.2
Wheat flour	2.7
Rice	2.4
Bacon	1.0

FOOD IN WHICH BASE-FORMING ELEMENTS PREDOMINATE

	Estimated excess base-forming elements to c.c. Normal alkali per 100 calories.
Celery	40.0
Cabbage	10.0–13.6
Potato	9.0–12.0
Prunes	7.9
Turnips	6.6–12.5
Apples	5.0
Milk	3.3
Beans	2.9– 6.8
Peas	1.9
Corn (entire grain)	0.8

Attention should be called also to the necessity of feeding a diet relatively rich in calcium and magnesium. The following table gives the amount of these elements in various of the commoner food-stuffs:

CALCIUM AND MAGNESIUM IN FOOD MATERIALS

	Ash in per cent. of substance.	MgO per cent. of ash.	CaO per cent. of ash.
Beef	.....	15.2	2.9
Egg-white	.....	13.0	13.0
Egg yolk	.....	6.0	38.0
Human milk	.....	5.0	24.3
Cows' milk	.....	20.0	151.0
Cocoa	4.9	15.9	2.8
Cornmeal	.....	14.9	6.3
Rice	0.67	13.4	0.8
Nuts	.....	13.0	8.6
Wheat flour	2.3	10.9	2.2
Barley	2.5	9.6	3.5
Apples	0.27	8.7	4.0
Peas	2.6	8.1	5.1
Oatmeal	2.3	7.0	3.0
Potatoes	5.0	2.5	0.8
Grapes	2.25	8.8	36.9
Asparagus	6.4	6.3	15.9
Bananas	.....	8.8	12.5
Spinach	2.03	5.3	12.5
Cauliflower	8.8	....	21.7
Cabbage	11.6	3.7	12.6
Radish	6.4	3.5	8.8
Beans	3.1	6.5	8.6
Strawberries	.....	....	14.2
Carrots	5.4	2.3	5.6

Exercise should be advised, but overexertion must be avoided. Besides the bowels, care must be taken of the skin and the kidneys. Frequent bathing and occasional sweating may be commended. An occasional alkaline diuretic may be administered if the action of the kidneys is sluggish.

2. Under this heading, "the treatment of the cause," the discussion must be very limited. Any rational therapeusis that tends to ameliorate or cure the diseased state underlying the acidosis condition is the proper course to pursue. If the condition of the tubercular patient is improving, for example, the

general state of the body will improve. It is obvious, therefore, that to reduce the excess H′ ion concentration due to nephritis or typhoid fever, etc., the main line of action should be directed against these diseases, and the H′ ion concentration will take care of itself. The diet, the climate, and the rest, etc., in tuberculosis; the diet, the purging, the diaphoresis, etc., in nephritis; the diet, the rest, the bathing, etc., in typhoid fever, and so on, and the improvement of the patient thereon will evince itself in the return to normal of the H′ ion concentration of the body fluids.

3. In cases of true acidosis, in contradistinction to those of the ketosis type, it is advisable to administer alkalies in the form of sodium bicarbonate to increase the "tampon" action of the blood. This alkali should be administered in dilute form to avoid irritation of the alimentary tract and to favor the ingestion and absorption of large quantities of fluids. The alkali may be prescribed in the form of Celestines, Vichy, a quart bottle of which contains 4 gm. of sodium bicarbonate. To this quantity of Vichy 5 gm. more of the bicarbonate may be added.

The alkalis may be the following: sodium bicarbonate, potassium bicarbonate, sodium citrate, magnesium citrate, and the salts of calcium. Sodium carbonate is too irritating and should not be used. Chalk or calcium carbonate is valuable for two reasons: first, it is a good alkali, and second, it tends to render the bicarbonate of soda less irritating to the gastric mucosa, thus avoiding the nausea or diarrhea.

The alkalis may be administered by rectum in the form of a 3 per cent. solution of sodium bicarbonate in normal saline. If, in extreme cases, intravenous injections are recommended, one may use a 3 per cent. solution of this alkali in normal saline in quantities up to 1000 c.c.

4. Stimulating the excretion of acids may be accomplished by the ingestion of large volumes of fluids, by the proper control of bowel movements, by diuresis, and by diaphoresis. Violent cathartics ought to be avoided. An alkaline salt may be administered on occasion. The alkaline diuretics may be used.

5. Treatment of ketosis.

In the treatment of diabetes careful attention should be paid to the state of fat tolerance, and all measures should be taken to avoid the oncome of the state of ketosis. This can be done by the improvement of the patient's tolerance for carbohydrates, by the elimination from the diet of substances that favor the formation of ketones, and by the administration of substances that upon catabolizing facilitate the combustion of the acid substances.

If we find that a state of ketosis exists, the most obvious treatment must be directed toward the curing, if possible, of this acidosis. Recourse must be had to the following principles: (1) The amount of fat intake must be reduced to a minimum, and (2) the carbohydrate oxidation must be stimulated because of its antiketogenic influence.

The patient is, therefore, put upon a diet extremely poor in fat and rich in vegetables and proteins, with the addition of a cereal, like oatmeal, which adds to the carbohydrate content. If absolutely necessary a thin slice of bread may be added to facilitate the proper oxidation of the fats. Sometimes a few doses of whisky well diluted with water increases the oxidation powers of the body and exerts an antiketogenic effect. It is not advisable to administer sodium bicarbonate for several reasons. Clinically, sodium bicarbonate seems to have only a deleterious influence. It very often is the final propulsion that induces coma. I have never seen a case of diabetic intoxication that was saved by the administration of bicarbonate of soda. I have, however, seen many patients in whom coma was induced immediately after the injudicious use of the sodium salt. Frequently the acetone substances lie dormant in the tissues of the body, in union with some protein or amino-acid group. The sudden flushing of the system with the sodium bicarbonate serves to split off the ketone substances with the immediate overwhelming of the vital centers. Joslin very properly states, "I believe that often a patient threatened with diabetic coma is sent into actual coma by the careless administration of alkalis."

Another danger of the ingestion of large quantities of alkalis is the extra work thrown upon the kidneys in the excretion of

large amounts of acids, so that the renal apparatus may cease to act. I have seen quite a number of diabetic patients who upon administration of the bicarbonate developed marked edema of the extremities, back, and face, which was relieved only by the interdiction of the use of the salt.

The constant excretion of acids from the body is a great drain upon the mineral reserve of the organism, and as Van Slyke has pointed out, it is not only the acids remaining in the body which might do harm, but also those excreted in the urine by the removal of the bases. "It is by no means, therefore, writes Joslin, "an unmixed blessing to favor the removal of acids from the body by the use of alkalis."

Now, in order to give a brief résumé, the following rules are to be followed in the treatment of ketosis:

(*a*) The bowels must be kept open, preferably by enemata, in order to avoid diarrhea and the consequent drainage of alkali salts from the body.

(*b*) Administer fluids in liberal amounts—a glass of liquid every hour or hour and a half.

(*c*) Increase the tolerance for carbohydrates.

(*d*) Avoid substances that induce the formation of the acids, such as fats, and often proteins.

(*e*) Administer substances which favor the combustion of ketones, as, for example, oatmeal, levulose, alcohol, etc.

(*f*) Do not prescribe alkalis.

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GLANDULAR FEVER

History; Full Description of Symptoms; Complications; Illustrative Cases; Management and Treatment.

GLANDULAR fever is an acute infectious disease characterized by sudden onset and an acute course, with fever and swelling of the cervical lymph-nodes, and terminating usually by crisis.

The condition was first fully described in 1889 by E. Pfeiffer, who claimed it to be a distinct and independent disease entity. Filatow had previously made brief reference to it. Hochsinger, Schleissner, and Neumann subsequently made valuable contributions to the subject. Many observers have taken issue with Pfeiffer on his claim that the condition was a nosologic entity and, to the present day, the question of the existence of a glandular fever *sui generis* is still a debated one, and its position in the medical literature is far from established. In many of our text-books the condition receives no recognition at all, and in none, except the most encyclopedic, is there more than mere mention of it. Park West in 1896 described rather fully an epidemic occurring in this country. His statistics covered 96 cases.

In the past two years I have observed 6 cases. I have used these as the basis for the following description:

Clinical Picture.—The onset of the disease is sudden. The child complains usually of headache and pain in the extremities. Nausea is frequently present, and occasionally vomiting. The temperature rises rapidly to about 104° F. Examination of the patient about this time usually reveals a single lymph-node about the size of an almond situated just below the angle of the

jaw, as a rule on the left side, seldom on the right. The lateral deep cervical glands can be felt slightly enlarged, like a string of beads, on the posterior border of the sternomastoid muscle, and extending well up to the nucha.

In many cases the condition subsides by the second day, the temperature dropping to normal, and the general condition improving rapidly. In the more severe cases the temperature remains at about 104° F. for the second and third days, with morning remissions to about 101½° F. There is regularly an enlargement of the spleen, and very occasionally of the liver. In most of the cases the axillary and inguinal nodes become enlarged, the latter more regularly than the former. As each new group of glands becomes affected the temperature becomes elevated, and may reach as high as 105° F.

Nose and Throat.—In all of my cases there was a marked redness of the posterior pharyngeal wall. This was the one uniform finding in addition to the enlarged glands present in every single case. In two the redness was very intense and involved the faucial pillars. In both of these cases the tonsils and adenoids had been removed. In two of the cases there was some inflammatory process going on in the adenoid tissue of the nasopharynx, as evidenced by discharge from the nose, obstructed breathing, and mucopus dropping from the posterior nasopharynx. In two instances the tympanum was found moderately injected, but with appropriate treatment the inflammation promptly subsided.

Lungs.—In 4 cases cough was a prominent symptom. It was invariably an unproductive and irritating cough. At times it was markedly spasmodic and resembled croup. There was never evident any change in the bronchi or lungs to account for it, and I feel inclined to believe that it was due to enlarged retrotracheal and bronchial nodes.

Heart.—The rate was usually slow in relation to the height of the temperature. I saw several patients with a fever of 104° F. or more, and a pulse-rate of between 100 and 110. In one case there was a soft systolic murmur which disappeared during convalescence and was probably hemic in origin.

Gastro-intestinal.—Constipation was present in every case. It was usually obstinate, and persisted until the crisis, or even beyond. I have never observed the critical discharges from the bowel mentioned by some authors. Nausea was quite regularly present at the onset, and occasionally vomiting. There was a marked anorexia which, unless it was overcome by forced feeding, usually led to intense emaciation.

Abdominal discomfort is frequently referred to as a characteristic feature of the disease. I observed it in only one case. It was not very marked, and lasted only for the first two days of the illness.

Liver.—In one case, after the third day, the liver could be palpated about 2 or 3 cm. below the costal margin. In none of the other cases was there any evidence of enlargement of the liver.

Spleen.—In every case observed the spleen was palpable at some time or other during the course of the disease. In 3 of the cases which started in most abruptly and with acute symptoms, the spleen was found enlarged at the first examination. In the others this finding was not present until the third or fourth day. The enlargement was never more than about 3 or 4 cm. below the costal margin. The spleen remained enlarged for at least two weeks, and usually three weeks or more.

Lymph-nodes.—The nodes, which are characteristically enlarged in this affection, are those situated along the posterior border of the sternocleidomastoid muscle, those situated at the nucha, and the single gland just below the angle of the jaw. The glands in front of the sternocleidomastoid muscle and those located beneath the muscle itself are frequently involved, but this is not characteristic, as they are often enlarged in other affections as well. In a large majority of the cases the swelling first appears on the left side of the neck. By the second or third day there is usually a swelling below the sternocleidomastoid muscle, about the size of a pigeon's egg, and the glands on the opposite side have begun to enlarge. The glands never fuse into masses, but remain perfectly discrete, and can be rolled about under the finger. They usually become quite tender and

painful. At the height of the disease the position of the head is similar to that in an acute torticollis, with the head inclined to and turned toward the affected side. The axillary and inguinal nodes quite regularly become enlarged. Except for a recrudescence of fever with the involvement of each new group of glands they seldom cause symptoms. The axillary glands subside quickly, as a rule, while the inguinal enlargement persists for several weeks. It would seem very probable that the tracheal and bronchial nodes are enlarged. This seems to be borne out by the persistent cough, often of spasmodic character, which is so frequently present. Occasionally substernal pain is present, and this too might very well be caused by enlarged bronchial nodes.

Complications.—*Nephritis.*—The most frequent complication is nephritis. This usually manifests itself from the second to the fourth week. There may be slight puffiness of the eyelids, with a trace of albumin and a few casts in the urine. The condition, as a rule, clears up after a few weeks.

Suppuration.—Neumann states that in one-half of the cases suppuration occurs. I have not seen it in any case. I consider the suppuration of the cervical glands an exceedingly rare occurrence in true glandular fever, and I think it should cast grave suspicion upon the diagnosis. I should be inclined to seek some primary focus in these cases, and I feel that most of them might be disposed of as other than cases of glandular fever. Not infrequently I have seen cases of suppurative lymph-adenitis in which the clinical picture closely resembled that of glandular fever. In each of these cases I was later impressed, upon more critical examination of the data, that one or more of the typical features of Pfeiffer's disease were absent. As a rule, in these secondary cases the anterior lymph-nodes were more involved than in the other condition and the general lymph glandular enlargement and palpable spleen are absent.

Emaciation.—This is a rather constant feature of the disease, and at times becomes so intense that we might almost consider it a complication. If the fever is at all protracted the patient presents a pitiable picture, with a total disappearance of the

subcutaneous fat, sunken eyes, and a marked pallor. There is usually a secondary anemia present as well.

Etiology.—*Sex.*—In the 27 cases reported by Neumann, 19 were boys and 8 were girls. In the 6 cases which I have seen, 3 were boys and 3 were girls.

Age.—The disease occurs almost exclusively in children between the ages of one and ten. Several cases occurring in infants are reported in the literature, and an occasional case in adults; the latter, however, are certainly very rare.

The ages in my cases were as follows: two, four, five, five, seven, and eight years.

Seasonal Incidence.—All of my cases occurred during the months of February, March, and April. This is in accord with most of the reported cases.

Epidemicity.—The disease is unquestionably contagious, but its extension seems to be limited to the house or household in which the case occurs. The most usual type of extensive epidemic is in garrisons or institutions where crowding favors its spread. There have, however, been several general widespread epidemics.

In my cases 2 occurred in one family and 3 in another.

Bacteriology.—Thus far no organism has been found associated with the disease with sufficient regularity to even suggest a causal connection. The most frequent finding has been a streptococcus cultured from the nose or throat, or from the pus of a suppurating gland.

Pathology.—Since Pfeiffer first described the condition there have been conflicting opinions as to the status of glandular fever as a nosologic entity. In favor of the unity of the disease, as opposed to a view of its being of secondary nature, are the following points: (1) Its epidemic character; (2) the temperature, the sudden onset of which and short and definite course with critical termination, suggest an acute infectious disease. In diphtheria, tonsillitis, rubella, measles, and scarlet fever we not infrequently see a marked glandular enlargement, but it is seldom or never associated with so great a rise in temperature as in this condition; (3) the early enlargement of the spleen and

occasionally of the liver. I have seen the spleen enlarged before there was any evidence of cervical adenitis. This would point to a general rather than a local infection; (4) the fact that in a great many cases the nasopharynx and the throat are clear, and, as in 2 of my cases, the adenoids and tonsils had been removed. This would make it appear to be highly improbable that these cases were secondary to an adenoiditis.

Those opposed to a view of the disease as an independent entity regard it as a variety of acute simple adenitis appearing epidemically in the course of a number of other conditions. Among the diseases most likely to give rise to it would be influenza or any epidemic inflammatory condition of the nasopharynx, the characteristic of these cases being that the inflammation of the glands becomes the most prominent feature.

The disease bears certain points of resemblance to scarlet fever, such as the angina, the cervical adenitis, and the nephritis which occasionally occurs during convalescence. Because of this it has been suggested that it is a form of scarlet fever without the rash. In this regard it might be noted that in 2 of my cases, which occurred in sisters, the father of the children had been in contact with a case of scarlet fever. The first of these children was striken with typical glandular fever. One week later the sister was taken down with what gave every evidence of being scarlet fever. The onset was sudden, with a temperature of 104° F., nausea, angina, and a scarlet rash over the face and chest.

It would seem not improbable that we are dealing here with a streptococcus, or some as yet unknown infection, which, entering by way of the throat, gives rise to an angina and later becomes localized, in scarlet fever in the skin, in glandular fever in the lymph-nodes; that is to say, we have an identical infection with varying localization.

The germ causing influenza has been thought to be a factor in the disease as well. In this regard it is interesting to note that the publication of Pfeiffer's paper was in 1889, when the great epidemic of influenza was at its height.

It has been suggested by Koplik that the portal of entry for

the infection is the gastro-intestinal tract, and on this basis he explains the usual involvement of the glands on the left side of the neck because of their proximity to the thoracic duct.

There have been no histologic studies made of the glands in these cases because of the rarity of a fatal termination.

Prognosis.—The prognosis is always good as to recovery. However, the general health and the vitality may be seriously impaired, particularly in the protracted cases. A few cases with fatal outcome have been reported due usually to a complicating nephritis.

Treatment.—Bed rest is indicated as long as the temperature is elevated. Strict isolation should be insisted upon if there are other children in the household.

For the fever hydrotherapeutic measures should be used. An ice-bag or a hot compress over the swollen glands is usually very grateful.

An initial calomel catharsis is advisable, and later the milder cathartics, particularly milk of magnesia, should be used to relieve the constipation.

Tonic measures should be used during convalescence, especially the syrup of iron iodid. Forced feeding, air, sunshine, and, if possible, a short stay at the seashore are valuable in restoring the child to health.

The following are abstracts from the histories of 3 of my cases, which give a fair description of the average case:

B. S. The patient is a girl of seven, the daughter of a schoolteacher.

Previous History.—Whooping-cough and chicken-pox. Has been a fairly healthy child, though not particularly robust. Tonsils and adenoids removed two years ago.

Present Illness.—Onset was sudden, with a rapid rise of temperature to 103½° F. and severe headache. A feeling of tightness in the throat was complained of and some difficulty in swallowing was present. There was slight nausea, but no vomiting.

Physical examination showed a rather puny child; skin and mucous membranes very pale; nutrition poor. There is no

discharge from the nose and the breathing is unobstructed. The throat shows a well-marked redness affecting the posterior pharyngeal wall, and extending well forward to the faucial pillars. The tonsils have been removed. The tongue is badly coated and furred. At the angle of the jaw, on the left side, there is a single gland, about the size of an almond, smooth and fairly movable, and but slightly tender. Along the posterior border of the sterno-cleidomastoid muscle there is a row of glands but slightly larger than buckshot, and extending the entire length of the muscle. The thoracic organs give no evidence of pathologic change. The liver is not palpable, and its upper border, as localized by percussion, is normally situated. The spleen is distinctly palpable about 2 cm. below the costal margin. No axillary or inguinal lymph-nodes are palpable.

Blood examination: Leukocytes 10,000; 80 per cent. polymorphonuclears.

Urine: Negative.

On the second day the patient seemed more sick than when first seen. The expression of the face was anxious. The head was turned so that the chin pointed to and was inclined toward the affected side. Just below the angle of the jaw on the left side there was a distinct swelling about the size of a plum, and situated beneath the sternomastoid muscle at this point a group of about three or four glands were palpable, freely movable, firm, and exceedingly tender. On the right side the posterior cervical glands were enlarged. In the axilla and in the groin several small glands were palpable. The temperature continued for eight days, rising each evening to between 101½° to 102½° F., and with a morning remission to about 100° F. As each new group of glands became affected the temperature rose to over 102° F., usually dropping on the following day. At the end of the tenth day the swelling of the nodes quite suddenly subsided, and the fever remained below 100½° F. The patient was emaciated for several weeks. The affected glands were still palpable, though small and not tender.

M. S. Girl, five and a half years; sister of the patient described in the preceding report.

Previous History.—Chicken-pox one year ago. Adenoids and tonsils removed two years ago.

Present Illness.—The patient had been exposed to contagion from her sister about eight days previous to the onset. While up and about she quite suddenly complained of feeling sick in the stomach and of headache. The temperature was taken at this time and was 104° F. The pain on swallowing was marked.

Physical Examination.—The patient, a robust child, appears acutely ill. The face seems somewhat puffy, and is covered by a deep, scarlet flush, particularly about the eyes, and extending down on the neck and chest. The area of redness stops abruptly about 1 cm. before the hair line, leaving a distinct white border. The throat shows a marked redness of the posterior pharyngeal wall and the faucial pillars, but no exudate. The heart and lungs are negative. The liver is not enlarged. The spleen is just palpable below the free border of the ribs. On each side, at the angle of the jaw, a single gland is palpable; and on the left side the glands along the posterior border of the sternomastoid are swollen.

The temperature lasted for three days, dropping suddenly without further developments. The child made an uneventful recovery. There was no desquamation.

M. C. The patient is a boy of five and a half years.

Previous History.—No serious illness.

Present Illness.—The onset was sudden, with fever and pain on swallowing. The temperature reached 105° F. on the first day of the illness and remained high, with but slight remissions, for forty-eight hours. It then began to subside, and by the end of the second week was normal, except for slight and variable elevations to about $100\frac{1}{2}$° F. for a period of about two weeks. The throat was distinctly reddened, the posterior pharyngeal wall being most affected. The spleen was found enlarged at the first examination, before there was any definite swelling of the cervical nodes. After forty-eight hours there was a well-marked swelling of the glands on the left side of the neck. The glands on the right side became swollen on the fourth day, but never became so swollen as those on the opposite side. The

axillary and inguinal glands became slightly enlarged. On the third day it was noted that the child's speech was thick and there was a slight coryza.

The blood-count was 12,000 leukocytes; 85 per cent. polymorphonuclears; 12 per cent. small lymphocytes; 2 per cent. large lymphocytes; one eosinophil.

At the end of the second week there was a puffiness of the eyes, and at this time the urine showed a trace of albumin and a few hyaline casts. This condition cleared up promptly. The swelling of the glands persisted for about three weeks, and then gradually subsided.

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